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Clinical Observational Study of the Novel Anti-Seizure Medication Perampanel as Add-On Therapy for Refractory Epilepsy in Pediatric Patients Aged 0-18 Years: Postprint

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Abstract

Background: Currently, the treatment of pediatric refractory epilepsy (RE) remains a challenge in epilepsy management. Perampanel (PER) is still a relatively new drug for treating pediatric RE in China, and there is currently a lack of recommendations for PER as add-on therapy for pediatric RE. Moreover, the sample sizes of RE pediatric patients treated with PER in domestic reports are relatively small. Therefore, the efficacy of PER for pediatric RE, particularly in younger children, still requires further investigation with larger sample sizes.

Objective: To investigate the efficacy, potential indications, adverse reactions, and tolerability of PER as add-on therapy for pediatric RE.

Methods: A self-controlled, retrospective analysis was conducted on RE pediatric patients aged 0–18 years who were diagnosed and treated at Qingdao University Affiliated Women and Children's Hospital from January 2022 to January 2023. Changes in seizure frequency at different observation time points before and after PER add-on therapy were compared, the effective rate of PER was evaluated, adverse drug reactions and drug retention rate were recorded, and clinical characteristics were analyzed between the PER effective group and ineffective group.

Results: A total of 192 subjects were included. After PER add-on therapy, the effective rates at weeks 12, 24, and 36 were 56.3% (108/192), 62.1% (113/182), and 69.7% (122/175), respectively, and the seizure-free rates were 19.3% (37/192), 21.4% (39/182), and 24.6% (43/175), respectively. The incidence of adverse reactions was 16.1% (31/192), mainly consisting of dizziness, irritability, fatigue, somnolence, etc. The drug retention rate at the last follow-up was 91.1% (175/192). When RE pediatric patients receiving PER add-on therapy had been continuously medicated for 12 weeks, there were statistically

significant differences between the effective and ineffective groups in age at onset, duration of antiepileptic treatment, origin type, seizure type, seizure frequency before PER add-on, number of concomitant antiseizure medications (ASMs), and ketogenic diet/surgical treatment status ($P<0.05$). Additionally, 178 patients underwent electroencephalogram (EEG) examination and 167 patients underwent cranial magnetic resonance imaging (MRI) examination; there were statistically significant differences in EEG findings and cranial MRI findings between the effective and ineffective groups ($P<0.05$). Among EEG findings, discharges in the anterior brain regions (frontal, central, anterior temporal, and mid-temporal) showed higher effective rates. Among cranial imaging findings, normal results were associated with higher effective rates, followed by patients with white matter injury as the main finding.

Conclusion: PER add-on therapy for pediatric RE demonstrates relatively high overall effective rates and retention rates, with mild adverse reactions and good drug tolerability. It is more effective for RE pediatric patients with later age at onset, motor seizures, focal origin, short duration of antiepileptic treatment, fewer concomitant medications, and lower seizure frequency. Higher effective rates were observed in patients with discharges in anterior brain regions (frontal, central, anterior temporal, and mid-temporal) on EEG and normal cranial MRI results.

Full Text

Clinical Observation of the New Antiseizure Drug Perampanel as Add-on Therapy for Refractory Epilepsy in Children Aged 0–18 Years

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Abstract

Background: The treatment of refractory epilepsy (RE) in children remains a major challenge in epilepsy management. In China, perampanel (PER) is a relatively new drug for pediatric RE, and there is currently a lack of recommendations for its use as add-on therapy in children with RE. Moreover, existing

domestic reports have involved relatively small sample sizes. Therefore, the efficacy of PER for pediatric RE, particularly in younger children, requires further investigation with larger samples.

Objective: To investigate the efficacy, potential indications, adverse reactions, and tolerability of PER as add-on therapy for pediatric RE.

Methods: We conducted a self-controlled, retrospective analysis of children aged 0–18 years with RE who were treated at the Affiliated Hospital of Women and Children, Qingdao University between January 2022 and January 2023. Changes in seizure frequency at different observation time points before and after PER add-on therapy were compared to evaluate the effective rate of PER. Adverse drug reactions and drug retention rates were recorded, and clinical characteristics were compared between PER-responsive and non-responsive groups.

Results: A total of 192 patients were included. After PER add-on therapy, the effective rates at 12, 24, and 36 weeks were 56.3% (108/192), 62.1% (113/182), and 69.7% (122/175), respectively. The seizure-free rates were 19.3% (37/192), 21.4% (39/182), and 24.6% (43/175). The incidence of adverse reactions was 16.1% (31/192), primarily dizziness, irritability, weakness, and somnolence. The drug retention rate at the final follow-up was 91.1% (175/192). After 12 weeks of continuous PER treatment, statistically significant differences were observed between responsive and non-responsive groups in age at onset, duration of antiseizure treatment, seizure origin type, seizure form, seizure frequency before PER add-on, number of concomitant antiseizure medications (ASMs), and ketogenic diet/surgical treatment status ($P<0.05$). Additionally, 178 patients underwent electroencephalography (EEG) and 167 underwent cranial magnetic resonance imaging (MRI). Significant differences were found in EEG and MRI findings between responsive and non-responsive groups ($P<0.05$). EEG showed higher efficacy in patients with discharges in the anterior brain regions (frontal, central, anterior temporal, and mid-temporal). MRI results showed higher efficacy in patients with normal imaging, followed by those with white matter injury.

Conclusion: PER add-on therapy for pediatric RE demonstrates high overall efficacy and retention rates, with mild adverse reactions and good tolerability. PER is more effective in RE children with later onset age, motor seizures, focal origin, shorter duration of antiseizure treatment, fewer concomitant ASMs, and lower seizure frequency. Patients with anterior brain discharges on EEG and normal MRI findings show higher response rates.

Keywords: Refractory epilepsy; Child; Perampanel; Treatment outcome; Adverse drug reactions

1. Materials and Methods

Perampanel is a highly selective, non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist and is currently the only drug with this mechanism approved for treating pediatric epilepsy. It holds unique significance in exploring new treatments for RE. PER was approved by China's National Medical Products Administration (NMPA) in 2019 for add-on treatment of focal-onset seizures (with or without secondary generalization) in children and adults aged 12 years and older. In 2021, NMPA expanded its indication to include monotherapy for children aged 4 years and older. While international studies have demonstrated clear efficacy of PER in adults and older children with focal epilepsy, its effectiveness as add-on therapy for pediatric RE remains controversial and inconsistent. Although some domestic and international applications have been reported, sample sizes have generally been small. This study reports on 192 children aged 0–18 years with RE treated with PER add-on therapy to provide clinical evidence for RE management in China.

1.1 Study Subjects

We retrospectively selected children with epilepsy who were treated at the outpatient clinic or inpatient department of Qingdao University Affiliated Women and Children's Hospital between January 2022 and January 2023. Inclusion criteria were: (1) age 0–18 years; (2) meeting the 2010 International League Against Epilepsy (ILAE) definition of refractory epilepsy, which requires failure to achieve seizure freedom for a sufficient duration (more than three times the longest pretreatment interseizure interval or one year) despite adequate trials of at least two tolerated and appropriately chosen ASMs; (3) more than two seizures in the three months before PER add-on; (4) no ASM adjustments in the month before PER add-on and PER treatment duration $ $3 months. Exclusion criteria were: (1) poor compliance or non-cooperation; (2) severe organ dysfunction or failure.

This retrospective study involved no intervention in patient diagnosis or treatment and was approved by the Medical Ethics Committee of Qingdao University Affiliated Women and Children's Hospital (approval number: QFELL-KY-2023-04).

1.2 Treatment Methods

PER tablets (Eisai Co., Ltd., Japan, 2 mg) were administered orally with the following starting doses: (1) 0.5 mg/day for children under 4 years or weighing <20 kg; (2) 1 mg/day for children aged 4 years and older weighing 20–30 kg; (3) 2 mg/day for children aged 4 years and older weighing >30 kg. The dose escalation interval was 2 weeks, with each increase equivalent to one starting dose, while other medications remained unchanged. Maintenance doses ranged from 2–8 mg/day, with a maximum of 12 mg/day. Specific starting doses, increments, and maintenance doses were individualized based on patient weight

and clinical status, with timely adjustments as needed.

1.3 Observation Indicators

Patient information was collected through outpatient and inpatient records, including: sex, age at onset, age at PER initiation, etiology, seizure characteristics in the three months before PER treatment (seizure origin, seizure form, seizure frequency classified according to 2017 ILAE diagnostic criteria, and epilepsy syndrome classification according to the ILAE Task Force on Nosology and Definitions 2022 series in Epilepsia), neuroimaging findings, and age at first PER use. Seizure outcomes at 12, 24, and 36 weeks after PER treatment, adverse reactions, and drug retention rates were recorded.

Efficacy assessment: Using the average seizure frequency in the three months before PER add-on as baseline, post-treatment efficacy was categorized as: (1) seizure freedom; (2) markedly effective: >75% seizure reduction; (3) effective: 50–75% seizure reduction; (4) ineffective: <50% seizure reduction; (5) worsening: >25% increase in seizure frequency. Seizure frequency reduction $ $50% was defined as overall effective.

1.4 Statistical Methods

SPSS 25.0 software was used for statistical analysis. Normally distributed continuous data were expressed as mean ± standard deviation ($\bar{x}\pm s$) and compared between groups using independent samples t-test, while paired t-test was used for before-and-after comparisons. Categorical data were expressed as percentages and compared using ^{2} test. Ranked data were analyzed using rank-sum test. $P<0.05$ was considered statistically significant.

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2. Results

2.1 General Characteristics

A total of 192 children with RE were included, comprising 107 males (55.7%) and 85 females (44.3%). The mean age at onset was $(4.5\$\pm3.3)years.Ageatfirst PERadd-onrangedfrom6monthsto18years, withameanof(7.9\pm3.6)years.Weightrangedfrom7–100kg, withameanof(3$ mg. Basic patient information is shown in Table 1 .

Etiologies included structural (81/192, 42.2%), genetic (24/192, 13.0%), metabolic (2/192, 1.0%), infectious (2/192, 1.0%), immune (2/192, 1.0%), and unknown (84/192, 43.8%). Seizure types included generalized, focal, or unknown-onset motor seizures (134/192, 69.8%), non-motor seizures (34/192, 17.7%), and both motor and non-motor seizures (24/192, 12.5%). Specific seizure forms are shown in Figure 1 [Figure 1: see original paper].

Genetic testing was completed in 29 patients, with abnormalities detected in 23 (23/192, 12.0%), including pathogenic variants in SCN1A, SLC13A,

TBC1D24, CACNA1, KCNB1, LAMA2, DOCK9, MAP2K1, TSC1, ALG11, POLG, PCDH19, SHARC, and PCDH19. A total of 27 patients (27/192, 14.1%) were diagnosed with specific epilepsy syndromes, including self-limited childhood epilepsy with centrotemporal spikes (SeLECTS, 12/27, 44.4%), Dravet syndrome (4/27, 14.8%), electrical status epilepticus during sleep (ESES, 3/27, 11.1%), Ohtahara syndrome (3/27, 11.1%), Lennox-Gastaut syndrome (2/27, 7.4%), febrile seizures plus (FS+, 2/27, 7.4%), and West syndrome (1/27, 3.7%). Intellectual disability or developmental delay was present in 57 patients (57/192, 29.7%), and 5 patients (5/192, 2.6%) had unclassifiable epileptic encephalopathy.

2.2 Clinical Efficacy

Seizure control at 12, 24, and 36 weeks after PER add-on therapy is shown in Table 2 . At the final follow-up, 122 patients achieved $ $50% seizure reduction, yielding an effective rate of 69.7% (122/175). Forty-three patients (43/175, 24.6%) achieved seizure freedom, while 11 patients (11/175, 6.3%) experienced increased seizure frequency.

After 12 weeks of continuous PER treatment, no statistically significant differences were observed between responsive and non-responsive groups in age, sex, epilepsy syndrome/encephalopathy status, age at first PER add-on, age categories at PER initiation, weight at first PER add-on, initial PER dose, maintenance PER dose, genetic testing abnormalities, or psychomotor developmental delay ($P>0.05$). However, significant differences were found in age at onset, duration of antiseizure treatment, seizure origin type, seizure form, seizure frequency before PER add-on, number of concomitant ASMs, and ketogenic diet/surgical treatment status ($P<0.05$) (Table 3).

Furthermore, 178 patients underwent EEG and 167 underwent cranial MRI. Significant differences were observed in EEG and MRI findings between responsive and non-responsive groups ($P<0.05$) (Tables 4 and 5). EEG showed higher efficacy in patients with discharges in anterior brain regions (frontal, central, anterior temporal, and mid-temporal) compared to posterior regions (occipital, parietal, posterior temporal). MRI results showed highest efficacy in patients with normal imaging, followed by those with white matter injury (20.7%, 19/92), while gray matter injury and developmental abnormalities showed lower rates (9.8%, 9/92 and 10.9%, 10/92, respectively).

Efficacy varied across epilepsy syndromes: SeLECTS showed the highest response rate (11/12, 91.6%), followed by ESES (2/3, 66.7%). FS+ showed 1 responder. Dravet syndrome (1/4, 25.0%) and Ohtahara syndrome had low response rates (1/3, 33.3%). Lennox-Gastaut syndrome and West syndrome showed no response (Figure 2 [Figure 2: see original paper]).

2.3 Adverse Reactions and Retention Rate

A total of 31 patients (31/192, 16.1%) experienced adverse reactions, with ages ranging from 2–16 years (22/31, 70.1% were over 6 years). Overall, 17 patients (17/192, 8.9%) discontinued PER, including 13 (13/17, 76.5%) under 6 years of age.

Discontinuation due to adverse reactions occurred in 5 patients (5/17, 29.4%). The most common adverse reaction was dizziness (8/31, 25.8%), followed by irritability (7/31, 22.6%), with 2 patients developing aggressive behavior requiring discontinuation. Other adverse reactions included rash, hyperexcitability, hyperhidrosis, and enuresis, all of which were generally tolerable and resolved spontaneously without intervention (Figure 3 [Figure 3: see original paper]).

Discontinuation due to lack of efficacy occurred in 11 patients (11/17, 64.7%), including 5 with epileptic spasms (2 with CACNA1E and ALG11 variants), 2 with absence seizures, 2 with automatisms (averaging 1 seizure daily), 1 with clonic seizures, and 1 whose seizures evolved from myoclonic to spasmodic episodes (occurring >10 times daily). One patient discontinued due to increased seizure frequency (worsening), experiencing generalized tonic-clonic seizures with intellectual disability following viral encephalitis at age 9 years. This patient had normal EEG and MRI monitoring but seizure frequency increased from 1/month before PER to 5–6/month after PER, requiring switch to clonazepam combined with multiple ASMs.

Among discontinued patients, 10 (10/17, 5.2%) stopped treatment at 4–6 months and 7 (7/17, 3.6%) after 6 months. The drug retention rate at final follow-up was 91.1% (175/192).

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3. Discussion

Although novel ASMs continue to emerge, the proportion of children with RE has not decreased, and overall prognosis remains poor, making pediatric RE a persistent therapeutic challenge. PER, as a new ASM with a novel mechanism and high efficacy, offers a promising alternative for RE treatment. Its efficacy and influencing factors in pediatric RE require further investigation.

This retrospective clinical observation study demonstrated that PER add-on therapy achieved high overall efficacy (122/175, 69.7%) and seizure freedom rates (43/175, 24.6%). Comparison at 12 weeks of continuous treatment suggested PER is more effective in RE children with focal-onset motor seizures, later onset age, shorter antiseizure treatment duration, focal EEG discharges, and normal cranial MRI. PER showed high drug retention (175/192, 91.1%), mild adverse reactions, and few severe adverse events, indicating good tolerability.

Domestic and international studies report PER effective rates of 9.1–77.3% and

seizure freedom rates of 4.8–25.0%. Our findings are consistent with these reports. Current evidence regarding age effects on PER efficacy is inconsistent. Some studies suggest lowest efficacy in children under 6 years (9.1%), while others indicate better responses in patients over 12 years (53.7% vs. 50.0% in younger children) or no age-related differences. Our analysis found no significant differences between responsive and non-responsive groups in sex, weight, age at PER initiation, intellectual disability, initial dose, or maintenance dose at 12 weeks, suggesting these factors may not correlate with efficacy. However, significant differences were observed in age at onset (P=0.001) and antiseizure treatment duration (P<0.001), with responders showing later onset and shorter treatment duration. This implies that earlier onset and longer treatment history may predict poorer treatment response, guiding clinical decision-making.

International multicenter studies suggest PER efficacy does not differ significantly across seizure types and epilepsy subtypes but shows higher efficacy in focal motor seizures, progressive myoclonic epilepsy, genetic generalized epilepsy, and early infantile epileptic encephalopathy, with lower efficacy in Lennox-Gastaut syndrome. Our study found significant differences in seizure origin type, seizure form, and seizure frequency between responsive and non-responsive groups. Focal-onset motor seizures with frequency $ $2/month and concomitant ASM use <2 showed higher efficacy. Although epilepsy syndrome distribution did not differ significantly between groups (P>0.05), efficacy varied across syndromes: high efficacy in SeLECTS and its variants and ESES, but low or no efficacy in other syndromes. Previous research indicates Dravet syndrome, Lennox-Gastaut syndrome, West syndrome, and Ohtahara syndrome often present with spasmic seizures and show drug resistance. Our findings of low PER efficacy in these syndromes suggest caution when considering PER for spasmic seizure types. The limited number of specific syndrome cases in our study necessitates larger sample studies to clarify PER's relationship with epilepsy syndrome types.

RE etiologies often involve structural brain changes such as encephalomalacia, developmental abnormalities, and focal cortical lesions, making EEG and MRI important diagnostic and therapeutic evaluation tools. We analyzed pretreatment EEG and MRI findings. EEG patterns differed significantly between groups (P<0.05), with the responsive group showing higher rates of focal discharges, particularly in anterior brain regions (frontal, central, anterior temporal, mid-temporal) compared to posterior regions. MRI findings also differed significantly (P=0.032), with normal imaging being most common in responders, followed by white matter injury, while gray matter injury and developmental abnormalities were less common.

Adverse reactions reported in PER studies for pediatric RE include somnolence (1.7–24.6%), dizziness (5–31.5%), irritability/aggression (2.8–22.7%), ataxia (1.1–9.3%), and nasopharyngitis (14.6%), with dizziness, somnolence, and aggression being common reasons for dose reduction or discontinuation. Our adverse reaction rate was 16.1%, with dizziness (8/31, 25.8%) and irritability (7/31, 22.6%) being most frequent, including 2 patients who discontinued

due to aggressive behavior. This may relate to AMPA receptor inhibition interfering with mechanisms involved in rapid antidepressant effects. Regarding safety, although AMPA receptors play critical roles in brain function and PER has a narrow therapeutic window, studies suggest that at therapeutic doses, PER preserves most normal synaptic transmission, reducing side effects. One study in patients over 12 years showed good tolerability with PER doses of 2–12 mg/day, with better efficacy at $ $4 mg/day but increased adverse events or discontinuation at 12 mg/day. In our study, 3 patients developed dizziness when titrated to 8 mg/day, which resolved when reduced to 6 mg/day. Notably, all 5 patients who discontinued due to adverse reactions were under 6 years, suggesting younger children may be more susceptible to severe adverse reactions requiring discontinuation.

Limitations: As children are developing individuals, ASM selection requires special consideration. PER offers a new mechanism and high efficacy, providing a new option for RE treatment. However, our study had a relatively small sample size, lacked matched comparison of concomitant medications (potentially causing confounding bias), and included few cases of specific syndromes, limiting generalizability. Future multicenter, large-sample prospective studies are needed to explore PER's efficacy, adverse reactions, drug interactions, and factors influencing effectiveness and safety, and to clarify its applicability across different ages, seizure types, epilepsy syndromes, and genetic phenotypes to guide precision therapy for pediatric RE.

Author Contributions: MA Huping participated in study conception and design, data collection and analysis, statistical processing, and manuscript writing. REN Rong participated in data collection. HOU Mei participated in clinical implementation and protocol development. YUAN Aiyun proposed research objectives, study design, and was responsible for quality control, overall supervision, and manuscript review.

Conflict of Interest: The authors declare no conflicts of interest.

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