Efficacy and Safety of Perampanel in Super-refractory Status Epilepticus

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Abstract

Background: Super-refractory status epilepticus (SRSE) is a life-threatening neurological emergency with high morbidity and mortality. In SRSE, γ-aminobutyric acidergic drugs become less effective and glutamate plays a major role in seizure controlled. Perampanel is a novel anti-seizure medication (ASM) which acts as a non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) receptor antagonist to reduce glutamate-mediated postsynaptic excitation. Previous animal studies and a few case reports have suggested that it may be effective to treat SRSE. Data on the efficacy of perampanel in treatment of SRSE in humans are limit.

Objectives: To access efficacy and safety of perampanel in the treatment of SRSE.

Study Design: Retrospective cohort study

Materials and Methods: All in-hospital patients with SRSE in Ramathibodi hospital between 1st January 2017 and 31st August 2022 were enrolled. The baseline characteristics, modified rankin scale (mRS) at admission and discharge, seizure semiology, duration of SRSE termination, ASM and dosages were corrected.

Results: For one hundred and two patients with SRSE were included. There was 40.2% of patients received perampanel as add-on treatment. The average initial and maximum dose were 4.5 mg/day and 10.5 mg/day, respectively. The time to SRSE controlled were 77 hours in perampanel group and 72 hours non-perampanel group, with p-value 0.142. This represented that no difference on efficacy of seizure cessation compared to non-perampanel group. The time from initial perampanel administered to SRSE controlled was

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26 hours. The persistent vegetative stage found in 34.2% in perampanel group compared with 40.9% in non-perampanel group. No serious adverse events were reported.

Conclusions: Although, this study shows insufficient evidence to support the usage of perampanel in SRSE treatment. However, this requires further clinical studies to establish the appropriate timing, dosing, and titration that are efficacious and safe for SE.

Keywords: Super-refractory status epilepticus, Perampanel, Anti-seizure medication, Status epilepticus, AMPA receptor antagonist

Introduction

Super-refractory status epilepticus (SRSE) is defined as status epilepticus (SE) that continues for 24 hours or more after the onset of anesthetic therapy, including those in whom SE recurs while on proper anesthetic treatment or after withdrawal of anesthetic agents.[1,2] Timely and effective treatment of SE is critical in reducing morbidity and mortality. Therapy delay in SE leads to the development of SRSE. The alteration of gamma-aminobutyric acid-A receptor leads to progressive resistance to benzodiazepine (BDZ), excessive glutamate-mediated postsynaptic excitation, and subsequent development of SRSE.[3-5] Perampanel (PER) is a non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic (AMPA) receptor antagonist that demonstrates efficacy and safety in limited number of studies in SRSE. But, the timely administration of PER, and variability in the dosing of PER are varied among these studies. There is emerging evidence that PER may be a beneficial treatment for SRSE. The current level of evidence to support its use in SRSE is limited to small, and uncontrolled studies.[6,7] But, the timely administration of PER, and variability in the dosing of PER are varied among these studies, There is emerging evidence that PER may be beneficial treatment of SRSE. The current level of evidence to support its use in SRSE is limited to small, and uncontrolled studies.[8,9] Thus, we conducted a retrospective cohort analysis by retrieving the clinical and continuous electroencephalography (EEG) monitoring data from our confirmed SRSE cases. The aim of this study is to analyze and compare the efficacy and safety of PER between PER-group and non-PER group in the management of SRSE. We review key considerations in individuals when initiating PER in SRSE cases including time from seizure onset to first dose of PER, time from first dose of PER to seizure control, initial dosage of PER, and maintenance dose of PER.

Materials and Methods

Study design and data collections

From January 1, 2017 to August 31, 2022, we performed a retrospective cohort analysis on consecutive adult patients (age ≥ 18) who were diagnosed with SRSE at Ramathibodi Hospital. Baseline demographic data including age, sex, body weight, body mass index, and underlying diseases are collected. For data analysis of SE, we use the definition and classification of SE which is proposed by the International League Against Epilepsy (ILAE) Task Force. (REF) Data on axis: classification of SE, axis2: etiology, and axis3: EEG correlation are collected. SRSE is defined by ongoing seizures 24 hours post-initiation of anesthesia or reoccurring seizures after anesthesia is weaned. (REF) Salzburg criteria is used for the diagnosis of non-convulsive SE (NCSE). (REF) The usage of anti-seizure medications (ASMs), and

anesthetic agents in SRSE are retrospectively reviewed, as well as their impact on clinical outcomes. After enrolment, SRSE patients are divided into two groups based on PER administration for further analysis, PER group and non-PER group, respectively. SRSE patients who received PER are designated as perampanel group. If PER is not given, SRSE patients are categorized into non-PER group. The research protocol was approved by the Institutional Review Boards of Ramathibodi Hospital, Mahidol University (COA. MURA2022/533).

Outcome measurements

The primary outcome is to determine the efficacy of PER in treatment of SRSE between PER and non-PER group. The efficacy of PER is determined by time to seizure control, and SRSE termination. PER responders are defined as being clinically and electrographically seizure free with PER being the last ASMs used, and not developing recurrence of SRSE.

The secondary outcome is to analyse adverse effects of PER, and clinical outcomes including length of hospital stay, mRS before admission, and mRS at discharge. Cerebral Performance Category (CPC) score widely is used for the assessment for post-arrest neurologic function. The functional outcome in SRSE-associated hypoxic ischemic encephalopathy is defined based on CPC score. A CPC score of 1 indicated full recovery, 2 indicated moderate disability, 3 indicated severe neurological disability with preserved consciousness, 4 indicated comatose or vegetative state patients, and 5 indicated death.

Statistical analysis

Categorical variables are presented as percentages and compared by using Fisher's exact test. Continuous variables are presented as the mean ± standard deviation (SD), and compared by using two-sample *t*-test. Non-parametric continuous variables are presented as median and interquartile ranges (IQRs) using Mann-Whitney *U*-test. All proportions and *P* values are calculated based on variables with few missing data.

Results

From January 2014 to August 2022, a total of 102 SRSE patients were eligible for analysis. Baseline clinical characteristics and SE classification between PER group and non-PER group were summarized in Table1. A history of epilepsy was significantly higher in PER group (24.4% vs 3.3%). A history of acute CNS infection was significantly higher in PER group, (24.4% vs 3.3%). Overall, the data on SE classification did not reach statistically significantly between both groups. In axis1, the majority of our patients were diagnosed with convulsive SE, followed by non-convulsive SE with coma. In Axis 2, most of SRSE patients were diagnosed with hypoxic ischemic encephalopathy, following by remote brain pathology and systemic medical conditions, respectively. The usage of CEEG monitoring was not significantly different between PER (n=39, 95.1%) and non-PER group (n=53, 86.9%). The minority of SRSE patients did not have CEEG monitoring due to unavailability of EEG machine, and their medical conditions. In axis3, the majority of patients had interictal EEG during CEEG monitoring, PER (n=26, 63.4%) and non-PER (n=34, 55.7%). Ictal EEG finding was found in the minority of patients, PER (n=9, 21.9%) and non-PER (n=5, 8.2%). Ictal EEG were more likely to be found in PER group (21.9% vs 8.2%). In axis4, most of patients were elderly ≥ 60 years, and had cardiovascular risk factors including hypertension,

dyslipidemia, and diabetes mellitus, respectively. Timing of seizure onset to first ASM was significantly different between two groups with median (IQR) of 5(3.0-5.0) in PER group, and 7(5.0-40.0) in non-PER group, p= 0.018. Most of SRSE patients had diazepam as the first ASM, PER (n=32,78.1%) and non-PER (n=43, 70.5%. Levetiracetam was the most commonly prescribed as the second ASM in both groups. For the third ASM, the pattern of ASMs prescription was significantly different in both groups, as shown in Table 1. Interestingly, PER as the third ASM was prescribed in only 6 patients (14.6%). Thus, PER was considered as a late option in SRSE treatment and was the preferred choice if SE control was not achieved after failure of more than 3ASMs. The usage of anesthetic agent was not significant between both groups. The time to seizure control and secondary outcome did not reached statistically significant in both groups. The majority of them had high mRS at discharge. The mortality rate was not significantly difference between both groups, PER (n=24, 58.5%) and non-PER (n=27, 44.3%).

Table 1 Comparison of baseline characteristics of patients between perampanel group and non-perampanel group in super-refractory status epilepticus

Clinical characteristics	Perampanel group, n (%)	Non-perampanel group, n (%)	p-value
Total	41 (40.2)	61 (59.8)	
Age, years, mean (SD)	63.4 (18.3)	69.3 (16.2)	0.093
Female gender	27 (65.8)	32 (52.5)	0.179
Body weight, kg, mean (SD)	56.3 (16.8)	60.4 (15.4)	.211
Body mass index, kg/m², mean (SD)	22.5 (6.3)	23.8 (5.7)	0.287
Underlying disease			
Hypertension	30 (73.2)	44 (72.1)	0.908
Diabetes mellitus	16 (39.2)	19 (31.2)	0.411
Dyslipidemia	27 (65.9)	42 (68.9)	0.751
Chronic kidney disease	13 (31.7)	20 (32.8)	0.909
Cerebrovascular disease	14 (34.2)	20 (32.8)	0.886
Cardiovascular disease	12 (29.3)	18 (29.5)	0.979
Epilepsy	12 (29.3)	6 (9.8)	0.012
Axis 1: Classification of SE			
Focal to bilateral convulsive SE	13 (31.7)	22 (36.1)	0.649
Generalized convulsive SE	29 (70.7)	40 (65.6)	0.585
Non-convulsive SE with coma	33 (80.49)	47 (77.1)	0.679
Axis 2: Etiology			
Systemic medical conditions	17 (41.5)	26 (42.6)	0.907
Hypoxic ischemic encephalopathy	33 (80.5)	47 (77.1)	0.939
Remote brain pathology	25 (60.9)	32 (52.5)	0.396
Acute CNS infection	10 (24.4)	2 (3.3)	0.001
Acute ischemic stroke	5 (12.2)	8 (13.1)	0.891
Acute intracerebral hemorrhage	3 (7.3)	9 (14.8)	0.352
Brain tumor	3 (7.32)	8 (13.1)	0.518
Axis 3: EEG correlation			
Used of continuous EEG monitoring	39 (95.1)	53 (86.9)	0.308
EEG findings			
Ictal EEG	9 (21.9)	5 (8.2)	0.048
Interictal EEG	26 (63.4)	34 (55.7)	0.440
No epileptiform discharge	5 (12.2)	15 (24.6)	0.122
Generalized suppression	3 (7.3)	7 (11.5)	0.489
Time of seizure onset to first ASM, minutes, median (IQR)	5 (3.0-5.0)	7 (5.0-40.0)	0.018

Table 1 Comparison of baseline characteristics of patients between perampanel group and non-perampanel group in super-refractory status epilepticus (cont.)

Clinical characteristics	Perampanel group, n (%)	Non-perampanel group, n (%)	p-value
The first ASM			0.339
Diazepam	32 (78.1)	43 (70.5)	
Midazolam	6 (14.6)	5 (8.2)	
Levetiracetam	3 (7.3)	10 (16.4)	
Valproic acid	0 (0)	1 (1.6)	
Phenytoin	0 (0)	2 (3.3)	
The second ASM			0.052
Levetiracetam	33 (80.5)	35 (57.4)	
Valproic acid	3 (7.3)	9 (14.8)	
Phenytoin	2 (4.9)	12 (19.7)	
Phenobarbital	1 (2.4)	0 (0)	
Lacosamide	2 (4.9)	3 (4.9)	
The third ASM			< 0.001
Levetiracetam	3 (7.3)	14 (22.9)	
Valproic acid	14 (34.2)	15 (24.6)	
Phenytoin	1 (2.4)	8 (13.1)	
Phenobarbital	3 (7.3)	2 (3.3)	
Lacosamide	13 (31.7)	8 (13.1)	
Perampanel	6 (14.6)	0 (0)	
Lamotrigine	0 (0)	1 (1.64)	
Topiramate	0 (0)	1 (1.64)	
Clobazam	1 (2.4)	0 (0)	
Type of anesthetic agents			0.023
Midazolam alone	33 (80.5)	43 (70.5)	
Midazolam and propofol	5 (12.2)	2 (3.3)	
Midazolam and sodium thiopental	1 (2.4)	2 (3.3)	
Time to seizure control, hours, median (IQR)	77 (50.0-120.0)	72 (40.0-96.0)	0.141
Hospital stays, days, median (IQR)	23 (14.0-50.0)	22 (14.0-47.0)	0.455
mRS before admission			0.344
mRS = 0	8 (19.5)	8 (13.1)	
mRS = 1	5 (12.2)	18 (29.5)	
mRS = 2	7 (17.1)	8 (13.1)	
mRS = 3	11 (26.8)	10 (16.4)	
mRS = 4	6 (14.6)	11 (18.0)	
mRS = 5	4 (9.8)	6 (9.8)	
mRS at discharge			0.294
mRS = 4	3 (7.3)	9 (14.7)	
mRS = 5	14 (34.2)	25 (40.9)	
mRS = 6	24 (58.5)	27 (44.3)	
The different between mRS before admission and at discharge			0.042
0-1	10 (24.4)	12 (19.7)	
2-3	15 (36.6)	22 (36.1)	
4-5	9 (21.9)	25 (40.9)	
6	7 (17.1)	2 (3.28)	
Death	24 (58.5)	27 (44.3)	0.157

ASM=antiseizure medication; CNS=central nervous system; EEG=electroencephalogram; IQR= interquartile range; kg=kilograms; kg/m²=kilogram per square meter; mRS=modified rankin score; SD=standard deviation; SE=status epilepticus

Of 102 SRSE patients, PER were prescribed in 41 patients (40.2%) and were not given in 61 patients (59.8%). The usage of PER in SRSE is shown in Table2. Time from seizure onset to first dose of PER were 45.5 hours (IQR 25.0-65.5). Time from first dose of PER to seizure control were 26 hours (IQR 16.0-65.0). The mean initial dosage of PER was 4.5 mg/day (±SD 2.3). The maximum dose of PER was 10.5 (±SD 5.1). No serious adverse events of PER were reported in our study.

Table 2 The usage of perampanel in super-refractory status epilepticus

Characteristics	Total n = 41 (%)
Time from seizure onset to first dose perampanel, hours, median (IQR)	45.5 (25.0-65.5)
Time from first dose perampanel to seizure control, hours, median (IQR)	26 (16.0-65.0)
Initial dose of perampanel used, mg/day, mean (SD)	4.5 (2.3)
Maximum dose of perampanel used, mg/day, mean (SD)	10.5 (5.1)
Used of perampanel with in third ASM	6 (14.6)

ASM=antiseizure medication; mg= milligrams; SD=standard deviation

We performed a subgroup analysis of HIE patients. The result was summarized in Table 3. PER was considered as a late option in HIE-associated SRSE treatment and was prescribed if SE control was not achieved after failure of more than 3 ASMs. The majority of them had high mRS, and high CPC at discharge.

Table 3 Subgroup analysis of HIE patients, comparison of baseline characteristics of patients between perampanel group and non-perampanel group in super-refractory status epilepticus

Clinical characteristics	Perampanel group, n (%)	Non-perampanel group, n (%)	p-value
Total = 22	9 (40.9)	13 (59.1)	
Age, years, mean (SD)	60.4 (15.3)	67.8 (8.2)	0.155
Sex			0.007
Male	2 (22.2)	11 (84.6)	
Female	7 (77.8)	2 (15.4)	
Body weight, kg, mean (SD)	58.1 (23.2)	64.4 (13.1)	0.432
Body mass index, kg/m², mean (SD)	23.5 (9.2)	24.5 (4.5)	0.752
Underlying disease			
Hypertension	6 (66.7)	8 (61.5)	1.000
Diabetes mellitus	3 (33.3)	5 (38.5)	1.000
Dyslipidemia	7 (77.8)	7 (53.9)	0.380
Chronic kidney disease	3 (33.3)	4 (30.8)	1.000
Cerebrovascular disease	2 (22.2)	4 (30.8)	1.000
Cardiovascular disease	6 (66.7)	3 (23.1)	1.000
Axis 1: Classification of SE			
Generalized myoclonic SE	7 (77.8)	13 (100)	0.156
Non-convulsive seizure with coma	4 (44.4)	7 (53.9)	1.000
Axis 3: EEG correlation			
Used of EEG continuous monitoring	9 (100)	11 (84.6)	0.494
EEG findings			
Ictal EEG	5 (55.6)	2 (15.4)	0.074
Interictal EEG	2 (22.2)	7 (53.9)	0.203
No epileptiform discharge	2 (22.2)	3 (23.1)	1.000
Generalized suppression	3 (33.3)	6 (46.2)	0.674

Table 3 Subgroup analysis of HIE patients, comparison of baseline characteristics of patients between perampanel group and non-perampanel group in super-refractory status epilepticus (cont.)

Clinical characteristics	Perampanel group, n (%)	Non-perampanel group, n (%)	p-value
Time of seizure onset to first ASM, minute, median (IQR)	5 (3.0-10.0)	5 (2.0-10.0)	0.733
The first ASM			1.000
Diazepam	8 (88.9)	11 (84.6)	
Midazolam	0 (0)	1 (7.7)	
Levetiracetam	1 (11.1)	1 (7.7)	
The second ASM			0.230
Levetiracetam	7 (77.8)	7 (53.9)	
Valproic acid	2 (22.2)	2 (15.4)	
Phenytoin	0 (0)	4 (30.8)	
The third ASM			0.130
Levetiracetam	1 (11.1)	4 (30.7)	
Valproic acid	3 (33.3)	6 (46.2)	
Phenytoin	1 (11.1)	1 (7.7)	
Phenobarbital	1 (11.1)	0 (0)	
Perampanel	3 (33.3)	0 (0)	
Type of anesthetic agents			0.591
Midazolam alone	7 (77.8)	9 (69.2)	
Midazolam and propofol	2 (22.2)	1 (7.7)	
Midazolam and sodium thiopental	0 (0)	1 (7.7)	
Time to seizure controlled, hours, median (IQR)	46 (36.0-96.0)	72 (48.0-85.0)	0.763
Hospital stays, day, median (IQR)	23 (7.0-40.0)	22 (15.0-44.0)	0.640
mRS before admission			0.891
mRS = 0	1 (11.1)	1 (7.7)	
mRS = 1	3 (33.3)	6 (46.2)	
mRS = 2	1 (11.1)	1 (7.7)	
mRS = 3	2 (22.2)	2 (15.4)	
mRS = 4	1 (11.1)	1 (7.7)	
mRS = 5	1 (11.1)	0 (0)	
mRS at discharge			0.074
mRS = 5	1 (11.1)	7 (53.85)	
mRS = 6	8 (88.9)	6 (46.2)	
The different between mRS before admission and at discharge			0.690
0-1	1 (11.1)	1 (7.7)	
2-3	3 (33.3)	2 (15.4)	
4-5	4 (44.4)	9 (69.2)	
6	1 (11.1)	1 (7.7)	
Cerebral Performance Category (CPC)			0.187
CPC = 4	4 (44.4)	10 (76.9)	
CPC = 5	5 (55.6)	3 (23.1)	
Death	8 (88.9)	6 (46.2)	0.074

ASM=antiseizure medication; EEG=electroencephalogram; HIE=hypoxic ischemic encephalopathy; IQR= interquartile range; kg=kilograms; kg/m²=kilogram per square meter; mRS=modified rankin score; SD=standard deviation

Discussion

This is a retrospective study for the evaluation efficacy and safety of PER in SRSE. For primary outcome, the efficacy of PER has measured by the comparison of time to seizure controlled with non-PER group. The result shown insufficient evidence to support the usage of PER in SRSE treatment. Limited number of participants, therapy delay in SE, long duration of SE before the administration of PER, as well as relatively low doses of PER, might be responsible for our result. PER could become a new therapeutic option in SE if PER is given during the established SE. For secondary outcome, PER has a satisfactory safety profile in SRSE. No cardiorespiratory or laboratory abnormalities were noted with PER treatment. There are no significantly difference of mortality rate and length of hospital stay between patient group who received and didn't received PER. The reasons of this insignificant result may be from the setting of SRSE that already known of high mortality rate. Comparison with previous PER trials, PER is not widely used in SE, RSE and SRSE in Thailand and frequently administered in an inadequate loading doses and titration, but in previous analysis and systemic review[4, 10-12] shown that PER had a positive benefit in SE cessation.

In subgroup analysis of HIE patients, the efficacy of PER was also no significantly difference. The mortality rate was significant higher in the group of patients received PER as add-on treatment in SRSE. These results may be from the high initial CPC scores, delayed administration and inadequate loading dose of PER. The morbidity seems to be no difference between groups, represented by mRS change from admission and discharge. There was no previous study efficacy of PER in patients with HIE who developed SRSE before.

The strength of our study includes the usage of the new ILAE 2015 definition and classification of SE, and the current definitions of different stages of SE.[15] This is a retrospective study that reviewed the practice on SE treatment that can point out the faults and improve in the future practice. This study provides early usage of novel ASM such as PER in SE, RSE and SRSE.

The first limitation of our study was less sample size, due to the nature of retrospective cohort study design and this present study was particular to only the small group of populations of SRSE. This may be affected power of the test in statistical analysis and the significantly results. Secondly, there were missing data such as the BW, BMI, timing of ASM administered and EEG findings, because of the data collections were retrospective by charts review.

Future application

A protocol for the treatment of SRSE focusing on the treatment strategies to control clinical and electroencephalographic epileptic activity is warranted. Strategies to evaluate treatment response and to wean drugs based on clinical results are also needed. PER could become a new therapeutic option in SE if PER is given during established SE. Further prospective studies are needed to establish the appropriate timing, initial dosing, and maintenance dosage of PER in SE.

Conclusion

This study shows insufficient evidence to support the usage of PER in SRSE treatment. Limited number of participants, therapy delay in SE,

long duration of SE before the administration of PER, as well as relatively low doses of PER, might be responsible for our result. Further prospective studies are needed to establish the appropriate timing, initial dosing, and maintenance dosage of PER in individuals with SRSE. PER has a satisfactory safety profile in SRSE. No cardiorespiratory or laboratory abnormalities were noted with PER treatment.

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