Efficacy and safety of adjunctive treatment with perampanel in epilepsy patients

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ABSTRACT

Introduction: Epilepsy is a neurological disease with high global prevalence. Almost one-third of epilepsy patients continue having seizures despite adequate treatment. Perampanel has been widely used in the Western countries as an adjunctive therapy for both generalized and focal seizures. Owing to its high cost, the use of perampanel is limited in our country.

Materials and Methods: We conducted a descriptive, retrospective study among epilepsy patients treated with perampanel. We aimed to assess the efficacy and safety of perampanel as an adjunctive in our hospital.

Results and Conclusions: From our cohort of 25 patients, most of the patients were either on one or three anti-seizure medications (ASMs) prior to initiation of perampanel. Perampanel was added in 88% of them due to persistent seizures. Twenty-two (88%) patients experienced reduction in seizure frequency. 12% experienced mild side effects, which were leg cramps, hyponatremia and drowsiness. Only 1 patient stopped perampanel due to its side effects.

Conclusion: Perampanel is a well-tolerated ASM that should be widely used as an adjunctive. More studies with regards to its efficacy and safety involving more centres are encouraged in Malaysia.

KEYWORDS:
Epilepsy, refractory, anti-seizure medication, perampanel, dizziness

INTRODUCTION

Epilepsy is a chronic brain disorder, characterised by two or more unprovoked seizures occurring more than 24 hours apart, due to the abnormal excessive or synchronous neuronal activity in the brain. The prevalence of epilepsy differs in different countries, ethnics, and socioeconomic statuses, with an overall lifetime population prevalence, worldwide, of 7.60 per 1,000.[1] The overall lifetime prevalence of epilepsy in Asian countries correlates with the worldwide data, varying from 1.5 to 14.0 per 1000 population, and it is reported as 7.8 per 1000 population in Malaysia.[2]

Treatment for epilepsy includes anti-seizure medications (ASMs), which are expected to achieve seizure freedom in 70% of patients. The remaining 30% of patients might need a substitution or an addition of a second ASM.[3] All ASMs can be categorised into broad- and narrow-spectra. Broad-spectrum ASMs such as valproic acid are commonly initiated in generalized or uncertain type of epilepsy; whereas narrow-spectrum ASMs such as carbamazepine and phenytoin are used in the treatment of focal seizures.[4] Recent years, many new ASMs with a wide variety of mechanisms of action were introduced with high hopes for a better seizure control. However, prospective audits on new ASMs such topiramate, levetiracetam, zonisamide, pregabalin, and lacosamide as an adjunctive therapy were disappointing with a low seizure freedom rate of less than 25%.[5]

Perampanel is one of the new ASMs introduced as an adjunctive therapy for epilepsy. It is a selective, non-competitive antagonist of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptors on post-synaptic neurons.[6] Many promising data were reported in the Western countries for the use of perampanel as an adjunctive therapy in refractory focal-onset seizures as well as generalized tonic-clonic seizures.[7-9] The commonly reported side effects of perampanel are dizziness, convulsion, and somnolence, which are statistically insignificant at low doses.[10] The utilisation of perampanel in the Asian population, especially in South East Asia is relatively low as compared to the Western countries, with limited information on its clinical performance and safety profile. More clinical studies are warranted for better cognizance of perampanel as an adjunctive treatment in the Asian population.

The aim of this study was to determine the change in seizure frequency and responder rate upon initiation of perampanel as an adjuntive ASM. We also studied the adverse events related to perampanel and the reasons for its discontinuation.

MATERIALS AND METHODS

This was a single-centre, descriptive, retrospective study done at the Hospital Canselor Tuanku Muhriz after obtaining approval of the Research Ethics Committee (Project Code: FF-2021-422). All patients with epilepsy treated with perampanel were included in this study. Those with missing data were excluded.

Twenty-five epilepsy patients treated with perampanel as an adjunctive therapy from January 2015 till December 2020

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Table I: Patients' demographic characteristics (n = 25)

Characteristics	n (%)
Ethnicity	
Malay	11 (44.0)
Chinese	12 (48.0)
Indian	1 (4.0)
Others	1 (4.0)
Age (year)	
0-20	3 (12.0)
21-40	11 (44.0)
41-60	9 (36.0)
61-80	2 (8.0)
Gender	
Male	17 (68.0)
Female	8 (32.0)
Medical diseases	
Metabolic	3 (12.0)
Brain related	3 (12.0)
Malignancy	1 (4.0)
Genetic	3 (12.0)
Autoimmune	1 (4.0)
None	14 (56.0)

Table II: Epilepsy characteristics (n = 25)

Characteristics	n (%)
Type of epilepsy	
Generalised onset	13 (52.0)
Focal onset	12 (48.0)
Unknown onset	0 (0.0)
Duration of disease (year)	
Less than one	2 (8.0)
1-10	10 (40.0)
11-20	8 (32.0)
21 and above	5 (20.0)
Aetiology	
Structural	5 (20.0)
Genetic	2 (8.0)
Infectious	5 (20.0)
Metabolic	1 (4.0)
Unknown	12 (48.0)
EEG	
Normal	3 (12.0)
Abnormal spikes	22 (88.0)
MRI	
Normal	14 (56.0)
Abnormal	11 (44.0)

were recruited from the Neurology Clinic of our hospital. The patients' demographics and characteristics of their seizures were collated in a data collection sheet.

The statistical analysis was performed using IBM Statistical Product and Service Solutions (SPSS) version 26.0. Descriptive statistics were used to present the variables recorded. We tabulated the descriptive statistics to summarize our data. Normally distributed data were expressed using mean ± standard deviation; whereas data that was not normally distributed were reported using median (inter-quartile range).

In this study, the efficacy of perampanel (seizure reduction) was taken as at least 50% reduction in seizure frequency compared to the baseline; whereas the safety of perampanel was measured as presence of any side effects among patients who were on perampanel.

RESULTS

A total of 25 patients had perampanel as an adjunctive ASM. Twelve (48.0%) were Chinese, 11 (44.0%) Malay and 1 (4.0%) each, were Indian and other races. The mean age (± standard deviation [SD]) of our patients was 37.5 years (± 13.4 years), with predominantly males (17, 68.0%). Eleven (44.0%) patients had other medical illnesses, which included metabolic diseases (3, 12.0%), brain related diseases (3, 12.0%), genetic diseases (3, 12.0%), malignancy (1, 4.0%) and autoimmune diseases (1, 4.0%) (Table I).

The mean duration of epilepsy in our cohort was 1.6 years (± 0.9 years). Regarding the types of epilepsy, they were almost equally distributed between generalised (13, 52.1%) and focal (12, 47.9%) epilepsy. The aetiology of epilepsy in most of our patients was unknown (12, 48.0%), while a small number were contributed by structural (5, 20.0%) and infectious (5, 20.0%) causes (Table II).

Table III: Perampanel and epilepsy (n = 25)

Characteristics	n (%)
Number of ASMs prior to perampanel	
1	7 (28.0)
2	6 (24.0)
3	7 (28.0)
4 and more	5 (20.0)
Indications for adding perampanel	
Persistent seizures with previous ASM	22 (88.0)
Side effects from previous ASM	0 (0.0)
Both	3 (12.0)
Changes in seizure frequency	
No change in seizure frequency	3 (12.0)
Seizure reduction[$]	22 (88.0)
Increase in seizure frequency	0 (0.0)
Duration on perampanel (year)*	
Less than 1	5 (23.8)
1-2	5 (23.8)
2-3	6 (28.6)
More than 3	5 (23.8)
Side effects from perampanel	
Yes[†]	3 (12.0)
No	22 (88.0)
Continuation of perampanel	
Yes	13 (52.0)
No	12 (48.0)
Reasons discontinuing perampanel (n = 12)	
Due to side effects	1 (8.3)
Others[#]	11 (91.7)

*4 missing data as patients died/defaulted follow up / transferred care to another hospital
[†]Side effects reported include leg cramps, hyponatremia, drowsiness.
[#]Other causes such as patients died or defaulted follow up.
[$]Seizure reduction refers to at least 50% reduction in seizure frequency from baseline (efficacy of perampanel).
ASM = Anti-seizure medication

Most of our patients were on at least one (7, 28.0%) or three (7, 28.0%) ASMs (mean ± SD = 2.4 ± 1.1) prior to the addition of perampanel. More than three-quarter (22, 88.0%) had perampanel added due to persistent seizures with previous ASMs. Three (12.0%) patients had both persistent seizures and side effects from the previous ASM, which led to the addition of perampanel. After adding perampanel, 22 (88.0%) experienced at least 50% reduction in seizure frequency from their baseline, and only three (12.0%) had no change in seizure frequency.

The mean (± SD) duration of perampanel use among our patients was 1.5 years (± 1.1 years). Only 3 (12.0%) complained of side effects, which were leg cramps, hyponatremia and drowsiness. Thirteen (52.0%) patients are still on perampanel; 1 (4.0%) on the other hand stopped treatment due to drowsiness. The remaining 11 (44.0%) patients were not on perampanel as they defaulted follow up or died (Table III).

DISCUSSION

Most of our patients with epilepsy are of Malay (11, 44.0%) and Chinese (12, 48.0%) ethnicity. This is representative of the national population whereby Malay and Chinese form the two largest ethnic groups in Malaysia. In the West, whites are more prone to having primary generalized epilepsy, whereas no racial differences were seen in temporal or frontal lobe epilepsy.[11] However in Malaysia, there are no recent studies to suggest ethnic preponderance towards types of epilepsy. Our epilepsy patients are predominantly male (17, 68.0%). This can be explained by the fact that they are more vulnerable to head injuries, stroke and CNS infections leading to seizures.[12]

Keezer et al., mentioned in their paper that almost half of the adults with epilepsy have at least one medical comorbidity. Diseases such as depression, dementia, anxiety, heart related diseases and peptic ulcer diseases are strongly related to epilepsy due it its bidirectional relations.[13] In our current cohort, they did not have any psychiatric or heart related issues.

When treating epilepsy, the gold standard is to use monotherapy at its most tolerated dose. Most of the time, a second or third agent is needed, thus achieving seizure freedom in more than half patients.[14] The average ASMs used by our patients were two ASMs, prior to addition of perampanel. Almost all of them had perampanel added due to persistent seizures and/or adverse effects from other ASMs. The recent PERaMpanel pooled analysIs of effecTiveness and tolerability (PERMIT) study showed that perampanel can be used as mono, or an adjunctive therapy to treat epilepsy, owing to its broad-spectrum properties.[15,16] The use of perampanel contributes to a significant reduction in seizure frequency, similar to our study in which up to 88.0% of the patients had seizure reduction.

Patients on perampanel commonly reported experiencing side effects, namely dizziness, fatigue, somnolence and irritability.[10] This was seen among those on perampanel 12 mg per day and the discontinuation rate among this group was as high as 5% due to its side effects. The incidence of dizziness among this group was as high as 20%.[17] One of our patients had to discontinue perampanel owing to dizziness affecting the daily activities.

Although the incidence is low, one of the most concerning side effects of perampanel is worsening of depression and aggression when not used in caution in patients with pre-existing psychiatric illness.[10] None of our patients suffered from any neuropsychiatric illnesses. We noted that one patient had hyponatremia secondary to perampanel. Hyponatremia caused by perampanel was rarely reported and the incidence is only less than 1% of general population.[18]

Our study has several limitations. The sample size was too small due to the high cost of perampanel, which most patients could not afford. This is a single-centre and retrospective study, the findings of which might not be generalizable. Many patients also lost to follow up while on perampanel.

CONCLUSIONS

Perampanel is a well-tolerated ASM that could be considered as an adjunctive treatment among epilepsy patients in Malaysia. More studies on the efficacy, retention rate and side effects of perampanel involving a larger population are encouraged.

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CONFLICT OF INTEREST

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