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Incidence and Factors Associated With More Than One Antiseizure Medications in Poststroke Epilepsy: A Single-Center Study

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Background: People with epilepsy are burdened with consequence of seizures, especially in drug resistant epilepsy. However, patients with poststroke epilepsy (PSE) who were mostly elderly and faced more seizures were affected not only by functional decline but also had no abundant time for antiseizure medication (ASM) trials.

Objective: To assess the incidence and factors associated with more than one ASMs in patients with PSE.

Methods: A retrospective chart review study was evaluated in 136 patients with a stroke onset following seizure with admission, who fulfilled the poststroke epilepsy diagnosis from January 2016 to June 2023. Then, they were categorized into only one and more than one ASMs groups to analyze.

Results: The incidence rate of patients with more than one ASMs in PSE was 89.0 persons and drug resistant PSE was 16.7 persons/1000 person-years. The median time to follow was 30 months and seizure latency was 7 months. The hemorrhagic stroke type was a factor associated with more than one ASMs compared with ischemic stroke (OR, 2.77; 95% CI, 1.23 - 6.23; $P = .01$). There was a multicollinearity effect in hemorrhagic stroke with cranial surgery during stroke events and underlying atrial fibrillation.

Conclusions: More than one ASMs in patients with PSE were applied in neurological practices per the incidence. Moreover, the hemorrhagic stroke was found to be associated with more than one ASMs.

Keywords: Poststroke epilepsy, Antiseizure medication, Associated factors, Drug resistant epilepsy

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Introduction

Cerebrovascular disease is the major cause of epilepsy in the elder.[1] People with epilepsy relate to morbidities in seizure, such as falls, injuries, head trauma, aspiration pneumonia, burns, or motorcycle accidents, and epilepsy, such as progressive cognitive impairment, or psychiatric illness. The epilepsy-related mortalities need to be recognized in routine situations such as drowning, motor vehicle-, falls-, and burns-related accidents, and status epilepticus.[2] Patients with poststroke epilepsy (PSE) and more seizure recurrence significantly related to more functional decline.[3]

Although there are predictive models for PSE both ischemic stroke as SeLECT scores[4] and hemorrhagic stroke as CAVE scores,[5] the models were developed in part of prediction for epilepsy related to the cerebrovascular cause, not for drug-resistant PSE or multiple antiseizure medication (ASM) therapy to control. However, there are shared factors in both models. The cortical abnormality in imaging is commonly recognized as the risk factor in epilepsy[6] and both models. The early seizure at stroke event is also revealed in both models. The severity of cerebrovascular diseases was categorized in the National Institute of Health Stroke Scale (NIHSS) score[7] for ischemic stroke and in hematoma volume more than 10 mL for hemorrhagic stroke. These shared factors might provide a trend to predict the seizure recurrence in PSE.

Moreover, the usual practice potentially added more ASM dosage and number to control the frequent seizures. The phenytoin was common ASM use lasted more than 10 years ago and levetiracetam was enlisted in our hospital drug list in 2014. Nevertheless, some patients were eventually classified drug resistant PSE.

Although PSE was common in neurological practice, drug resistant PSE was not usually recognized, in both practice and study. The proportions of drug resistant PSE in PSE were also varied in past studies, 4.5%,[8] 12.9%,[9] and 18.2%.[10] They were 12.8% in drug-resistant post-ischemic-stroke epilepsy,[10] and 22.6%,[11] 28.1% in drug-resistant post-intracerebral-hemorrhage epilepsy.[10] While the definition of drug resistant epilepsy required failure of adequate trials of 2 tolerated and appropriate ASM use,[12] PSE patients who were mostly elderly might have not enough time to participate in trial. Moreover, there is a gap between more than one ASM therapy and definition of drug resistant epilepsy. To ensure early awareness, the practice for seizure control should not only fulfil the definition of drug resistant epilepsy before treatment adjustment, but also address the limited study on the primary objective of more than one ASM treatment. So, patients with PSE who were clinically controlled by more than one ASMs were considered in this study to compare with only one ASM use.

This study aimed to assess the incidence and factors associated with more than one ASMs compared with only one ASM to control seizures in patients with PSE.

Methods

Participants

All 689 patients who had been diagnosed the stroke; both ischemic and hemorrhagic strokes, ASM had been concurrently prescribed in Chaophrayayommarat Hospital, Thailand, from January 2015 to June 2023 were enlisted.

The inclusion criteria were PSE patients who the occurrence of seizures more than 7 days after a stroke onset, aged 20 years and over, and no history of possible seizures before.

The exclusion criteria were the subsequent diagnosis of the other causes of epilepsy, lack of visits for more than 6 months, and insufficient data. Hence, 31 patients who were later diagnosed as the other causes of structural stroke categorized by the International League Against Epilepsy,[13] such as immune, infectious, or metabolic causes, and further 15 patients who were subsequently found malignancy conditions were excluded.

The antiseizure prophylaxis in hemorrhagic stroke, insufficient data, uncertain clinical seizures, and patients who subsequently revealed a history of seizure before the stroke event were also excluded.

Ethics

This study was approved by the Institutional Review Board of Chaophrayayommarat Hospital in Suphan Buri, Thailand (No. YM017/2566) on July 6, 2023.

Study Design

Baseline characteristics and potential risk factors in this chart review retrospective study were examined from their medical records who met the inclusion and exclusion criteria as described. History of alcohol drinking was defined as an estimated intake of more than one drink per week disclosed by patients or relatives and written in documents. The early seizures defined the onset of seizure following stroke event within 7 days and were not attributed to poststroke seizure. The poststroke seizures following epilepsy were clinical seizures with history from the patients and relatives and were admitted with final diagnosis by neurologists or neurosurgeons.

The severity of stroke was classified by NIHSS despite the ischemic and hemorrhagic stroke. The cortical involvement in noncontrast computed tomography of brain was reviewed both imaging displayed anatomical gray matter involvement and official reports by radiologists. The poststroke seizure latency was counted in months from the onset of stroke to subsequent seizure admission. The follow-up duration from the onset of stroke to the latest visit was also collected in months. Drug resistant PSE was defined as the combination of definition drug resistant epilepsy and PSE. The comorbidities included hypertension, diabetes mellitus type II, chronic kidney disease stage IV and V, coronary artery disease, and atrial fibrillations were reckoned at onset of stroke.

When the baseline characteristics were gathered, they were categorized into only one and more than one ASMs group for analysis.

Statistical Analysis

Fisher exact test and Mann-Whitney *U* test were used for statistical analysis of the categorical and continuous variable comparison, respectively, with statistical software, SPSS version 18.0 (PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc; 2009). Only age at stroke onset data, distributed as accepted normal, was analyzed by unpaired *t* test. A 95% confidence interval (CI) was set and power at 80%. A logistic regression analysis was done in binary and multiple variables, if univariate analysis expressed potential significance defined as *P* value less than .20, to predict multiple antiseizure medication use. Pearson's chi-squared test would be applied to prove multicollinearity if some variable results in univariate analysis showed potential.

Results

There were 136 patients who fulfilled the study criteria. The incidence rate of patients with more than one ASMs in PSE was 89.0 persons/1000 person-years. The proportion of patient with more than one ASMs in PSE patients was 23.5%. The median follow-up duration of each patient was 30 months. Mean age of stroke onset was 60.2 years, both only one and more than one ASMs groups (Table 1), and male predominance (64.0%). The hemorrhagic stroke type was more significantly found in more than one ASM group than only one group (56.3% vs 31.7%; $P = .01$). Neurosurgical procedures (craniectomy and craniotomy), during stroke event were also significantly showed in more than one ASM group ($P = .01$). The phenytoin use in only one ASM group was 56.5%, and current levetiracetam use in more than one ASM group was 96.9%. In comorbidities, most patients were found to have underlying hypertension (82.4%). The percentage of underlying atrial fibrillation in only one ASM group was 19.2%, compared to more than one ASM group was only 3.1% ($P = .02$).

To demonstrate the associated factors, hemorrhagic stroke type and cranial surgery during stroke were potential in multicollinearity. The Pearson's chi-squared test to reveal dependence was applied and supported as a multicollinearity effect ($P < .001$). The underlying atrial fibrillation factor was also dependent on the hemorrhagic stroke factor, by Pearson's chi-squared test ($P < .001$). All patients with underlying atrial fibrillation were

presented with ischemic stroke. Then, the hemorrhagic stroke factor was analyzed by binary logistic regression to confirm and revealed to be an associated factor of more than one ASMs in patients with PSE (Crude odds ratio [OR], 2.77; 95% CI, 1.23 - 6.23; P = .01)

The incidence rate of drug resistant PSE was subsequently calculated and showed 16.7 persons/1000 person-years. The proportion of drug resistance in PSE was 4.4% (6 patients). Levetiracetam was prescribed and well tolerated in these patients.

In subgroup analysis of hemorrhagic stroke for intracerebral hemorrhage; 34 patients, there was no significant difference in only one and more than one ASM groups for cortical involvement, aged less than 65 years, hematoma volume more than 10 mL, and early seizure within 7 days (Table 2).

Table 1. Baseline Characteristics in Poststroke Epilepsy Patients

Characteristic	No. (%)			*P* Value*
	Total (N = 136)	1 ASM Group (n = 104)	> 1 ASM Group (n = 32)	
Age at the stroke onset, mean (SD), y	60.2 (13.4)	60.2 (13.3)	60.2 (13.9)	.98
Female	49 (36.0)	38 (36.5)	11 (34.4)	.82
Alcohol consumption	34 (25.0)	27 (26.0)	7 (21.9)	.64
Hospitalizations during the stroke, median (IQR), d	8 (4.0 - 16.0)	8 (4.0 - 16.0)	8 (4.0 - 16.5)	.79
Hemorrhagic stroke	51 (37.5)	33 (31.7)	18 (56.3)	.01
Early seizure within 7 d	36 (26.5)	24 (23.1)	12 (37.5)	.11
Cranial surgery during the stroke	24 (17.6)	13 (12.5)	11 (34.4)	.01
Severity of stroke as NIHSS				
Mild severity (NIHSS ≤ 3)	44 (32.4)	30 (28.8)	14 (43.8)	.26
Moderate severity (NIHSS 4 - 10)	19 (15.4)	16 (15.4)	3 (9.4)	
Severe severity (NIHSS > 10)	73 (53.7)	58 (55.8)	15 (46.9)	
Cortical involvement	118 (86.8)	90 (86.5)	28 (87.5)	.89
Seizure latency, median (IQR), mo	7 (3.0 - 18.0)	8.0 (3.0 - 17.5)	7.0 (4.0 - 19.3)	.38
Follow-up duration, median (IQR), mo	30 (15.0 - 54.0)	30.5 (14.3 - 57.3)	30.0 (18.0 - 46.3)	.91
Current phenytoin treatment	82 (60.3)	59 (56.7)	23 (71.9)	.13
Current levetiracetam treatment	72 (52.9)	41 (39.4)	31 (96.9)	< .001
Current valproate treatment	15 (11.0)	0	15 (46.9)	< .001
Comorbidities				
Hypertension	112 (82.4)	89 (85.6)	23 (71.9)	.07
Diabetes mellitus type II	51 (37.5)	37 (35.6)	14 (43.8)	.40
Chronic kidney disease stage IV-V	4 (2.9)	3 (2.9)	1 (3.1)	.94
Coronary artery disease	13 (9.6)	9 (8.7)	4 (12.5)	.52
Atrial fibrillation	21 (15.4)	20 (19.2)	1 (3.1)	.02

Abbreviations: SD, standard deviation; IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale score.

* Potential significance defined as *P* value less than .05.

Table 2. Subgroup Analysis in Patients With Post Intracerebral Hemorrhage Epilepsy Based on CAVE Score

Characteristic	No. (%)			*P* Value*
	Total (N = 34)	1 ASM Group (n = 26)	> 1 ASM Group (n = 8)	
Cortical involvement	32 (94.1)	25 (96.2)	7 (87.5)	.42
Age < 65 y	27 (79.4)	22 (84.6)	5 (62.5)	.18
Volume of hematoma > 10 mL	26 (76.5)	20 (76.9)	6 (75.0)	.91
Early seizure within 7 d	11 (32.4)	9 (34.6)	2 (25.0)	.61

* Potential significance defined as *P* value less than .05.

Discussion

The incidence rate of patients with more than one ASMs in PSE was 89.0 persons/1000 person-years and drug resistant PSE was 16.7 persons/1000 person-years. The hemorrhagic stroke type revealed being the associated factor of more than one ASM use in patients with PSE. In subgroup analysis based on the CAVE score for hemorrhagic stroke; intracerebral hemorrhage, however, there was no significant association between more than one and only one ASM group among the small sample size.

The hemorrhagic stroke was the risk factor for PSE in meta-analysis[14] and drug resistant PSE.[10, 15] This study likewise supported the potential of seizure recurrence and risk factors of drug resistant PSE. The mechanical effect in expansion and sequelae of hemosiderin depositions with gliotic scarring[16] might affect the seizure recurrence in hemorrhagic stroke. Although ASM prophylaxis might reduce the early seizure for intracerebral hemorrhage for a week in a few studies,[17-19] the meta-analysis[20] and the practice guideline for management of intracerebral hemorrhage[21] still recommended against ASM prophylaxis, which could not control late-onset seizure, nor improve functional outcomes.

Cortical involvement was a risk factor for PSE in both hemorrhagic[2] and ischemic stroke models.[4] However, there was no impact in drug resistant PSE[10, 11, 15] as a result as the present study between only one and more than one ASM groups. This evidence might imply that the epileptogenesis in PSE and drug resistant PSE was hypothetically different.

The younger age of stroke had been proposed as a risk factor of drug resistant PSE[9, 22] in a mean follow-up duration of 3.86 years. The present study could not express the role of age as the associated factor. The mean age of stroke onset was 60.2 years, which was not different in both only one and more than one ASM groups. However, the time to follow might affect our study which median follow-up duration was 2.5 years. It needs to design the next prospective study to cover a longer duration.

While the shorter latency of seizure recurrence could affect the drug resistant PSE in other study,[15] the median seizure latency of the present study was 7 months, which was not different between only one and more than one ASM groups. However, most patients with intracerebral hemorrhage presented subsequent seizures within first years (61.8%), supported by past studies in which the risk of new-onset PSE was highest in the first year.[9, 23]

The status epilepticus at seizure or stroke onset has been markedly updated in risk of PSE[22, 24] and already recognized in drug resistant PSE.[10, 15] There was insufficient data in our medical records to confirm the status epilepticus diagnosis. However, the early seizure in 7 days during a stroke event in the present study could not reveal a significant difference despite presenting 37.5% in more than one vs 23.1% in only one ASM groups. The early seizure in the intracerebral hemorrhage subgroup was also not significant. The prospective cohort study can observe this factor to confirm the association. Moreover, the availability of electroencephalography to detect the nonconvulsive status epilepticus was an obstacle for our past situations.

Severity of stroke onset could not establish being the associated factors of PSE,[14, 23] it was also unclear in drug resistant PSE, both being the risk[10, 15] and not related[9, 11] as the present study. The evaluation of and classification of severity were varied in both ischemic and hemorrhagic stroke despite NIHSS scores applied. There were other classifications such as severe score (NIHSS ≥ 16),[10, 15] Canadian Neurological Scale (CNS) score,[9] Barthel index,[25] or applied hematoma volume in hemorrhagic stroke. These heterogenous data might affect the analysis.

The percentage of only one ASM group; 76.5%, was not only consistent with general practice which was mostly controlled by one ASM, but it was also supported by many studies. They showed 54% and 67% being seizure-free for at least 2 years,[8, 26] or 69% for a year,[27] 68% of PSE patients taking only one ASM,[26] and 87% for non-drug resistant PSE.[3] Even though one study[27] revealed patients with more than one ASMs was 94.1%, the current levetiracetam use was 81.7% compared with 39.4% in the present study. Furthermore, the primary objective of those studies[27, 28] confirmed the outcome that the newer-generation ASM use included levetiracetam affected less seizure recurrence and improved tolerance compared with the conventional ASM therapy, such as phenytoin or sodium valproate. There was no patient who started with sodium valproate in this study, all of 15 patients who had sodium valproate-adjunctive treatment were in more than on ASM group. However, levetiracetam therapy was increased in recent years and more prescribed which showed 96.9% usage in more than one ASM group.

There were some limitations. First, the seizure monitoring could not be reached properly in our medical records. Although the admission with a diagnosis as seizure was qualified, the seizure in the community could not be observed in this study. It was an indirect observation from ASM adjustment by doctors, which depends on caregivers who could not recognize the seizure event. Moreover, patient transportation to our urban hospital was difficult in some families, especially for severe sequelae of stroke event, the prescription of ASM also depended on relatives. Second, the strict criteria to confirm the diagnosis made some patients, as insufficient data, could not be included. These number might affect the result. Third, the cortical involvement was subjectively judged by the author and existing official reports. Fourth, patients with underlying atrial fibrillation were observed during a stroke event. Although all 21 patients who presented with ischemic stroke expressed a significant difference between only one and more than one ASM groups, there was only one patient in more than one ASM group. The number was too small to interpret. This facet might influence multicollinearity effect in atrial fibrillation and hemorrhagic stroke factors, also. Fifth, the small number of patients with post intracerebral hemorrhage epilepsy in the subgroup analysis was the main obstacle to its application.

The following prospective cohort studies to monitor seizure recurrence or functional decline for patients with PSE in systematized epilepsy clinic will affirm the factors related with more than one ASMs, including the efficacy of each ASM in only one ASM group, to warrant quality of life in patients with stroke related epilepsy.

Conclusions

The incidence rate of patients with more than one ASMs in PSE was 89.0 persons and drug resistant PSE was 16.7 persons/1000 person-years. The hemorrhagic stroke type was a factor associated with more than one ASMs, indicated to early aware and close seizure monitoring.

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อุบัติการณ์และปัจจัยที่เกี่ยวข้องกับการรักษาด้วยยากันชักมากกว่า 1 ชนิด ในผู้ป่วยโรคลมชักหลังภาวะหลอดเลือดสมอง: การศึกษาสถาบันเดียว

ก้าวหน้า สุขสุชะโน

กลุ่มงานอายุรกรรม โรงพยาบาลเจ้าพระยายมราช สุพรรณบุรี ประเทศไทย

บทนำ: ผู้ที่เป็นโรคลมชักจะได้รับผลกระทบต่อเนื่องที่เกิดขึ้นจากอาการชัก โดยเฉพาะโรคลมชักที่ดื้อต่อยา อย่างไรก็ตาม ผู้ป่วยที่มีโรคลมชักหลังภาวะหลอดเลือดสมอง ส่วนใหญ่เป็นผู้สูงวัยและต้องเผชิญกับอาการชักที่มากขึ้นนั้น ไม่เพียงแต่มีสมรรถนะที่แย่ลง แต่ยังไม่มีระยะเวลาเพียงพอสำหรับการเลือกทดลองใช้ยากันชักอีกด้วย

วัตถุประสงค์: เพื่อหาอุบัติการณ์และปัจจัยที่เกี่ยวข้องกับการรักษาด้วยยากันชักมากกว่า 1 ชนิด ในผู้ป่วยโรคลมชักหลังภาวะหลอดเลือดสมอง

วิธีการศึกษา: การศึกษาทบทวนเวชระเบียนย้อนหลังในผู้ป่วยที่เริ่มจากภาวะหลอดเลือดสมองแล้วตามด้วยอาการชักจนต้องรับการรักษาในโรงพยาบาล และวินิจฉัยเข้าได้กับโรคลมชักหลังภาวะหลอดเลือดสมอง จำนวน 136 คน ตั้งแต่เดือนมกราคม พ.ศ. 2559 ถึงเดือนมิถุนายน พ.ศ. 2566 จากนั้นวิเคราะห์เปรียบเทียบระหว่างกลุ่มที่ได้รับยากันชักเพียง 1 ชนิด และกลุ่มที่ได้รับยากันชักมากกว่า 1 ชนิด

ผลการศึกษา: อัตราอุบัติการณ์ของการรักษาด้วยยากันชักมากกว่า 1 ชนิด ในผู้ป่วยโรคลมชักหลังภาวะหลอดเลือดสมอง เท่ากับ 89.0 คน/1,000 คน-ปี และอัตราอุบัติการณ์ของผู้ป่วยโรคลมชักหลังภาวะหลอดเลือดสมองที่ดื้อต่อยา เท่ากับ 16.7 คน/1,000 คน-ปี ค่ามัธยฐานของระยะเวลาในการติดตาม เท่ากับ 30 เดือน ค่ามัธยฐานของระยะเวลาที่เกิดอาการชักตามมา เท่ากับ 7 เดือน ชนิดของโรคหลอดเลือดสมองแตกเป็นปัจจัยที่เกี่ยวข้องกับการรักษาด้วยยากันชักมากกว่า 1 ชนิด เมื่อ เทียบกับโรคหลอดเลือดสมองตีบหรืออุดตัน (OR, 2.77; 95% CI, 1.23 - 6.23; $P = .01$) ผลของสหสัมพันธ์ร่วมระหว่างตัวแปรแบบเส้นตรงเกิดขึ้นในตัวแปรโรคหลอดเลือดสมองแตกร่วมกับประวัติการผ่าตัดกะโหลกขณะเป็นโรคหลอดเลือดสมองและโรคหัวใจเต้นพริ้ว

สรุป: การรักษาด้วยยากันชักมากกว่า 1 ชนิด ในผู้ป่วยโรคลมชักหลังภาวะหลอดเลือดสมองเป็นการรักษาที่ถูกใช้ในเวชปฏิบัติระบบประสาทตามที่พบในอุบัติการณ์ อีกทั้งโรคหลอดเลือดสมองแตกยังเป็นปัจจัยที่เกี่ยวข้องกับการรักษาด้วยยากันชักมากกว่า 1 ชนิด

คำสำคัญ: โรคลมชักหลังภาวะหลอดเลือดสมอง ยากันชัก ปัจจัยที่เกี่ยวข้อง โรคลมชักที่ดื้อต่อยา

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