The incidence and associated risk factors of early poststroke seizures and poststroke epilepsy.

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Abstract

Objectives: To study the incidence of early poststroke seizure and poststroke epilepsy among Thai people and the differences in early poststroke seizures and poststroke epilepsy-associated risk factors.

Methods: This study was to study all patients who had poststroke seizures at the Faculty of Medicine Vajira Hospital between January 1, 2014 and December 31, 2018. The patients divided into two groups, including early poststroke seizures group and poststroke epilepsy group with a minimum follow-up of 6 months.

Results: There were 3,600 patients with no history of epilepsy presented with the first stroke. Ninety-three patients had developed seizures. Mostly, 54 patients (58.1%) were in a group of hemorrhagic stroke. For ischemic stroke patients, 39 patients (41.9%) had seizures occurred. There were 59 patients with an early poststroke seizure group, of whose 44 (74.6%) were hemorrhagic stroke patients, and 15 of them (25.4%) were ischemic stroke patients. For the poststroke epilepsy group, 34 patients found in which 24 patients among them (70.6%) were ischemic stroke patients, and 10 of them (29.4%) were hemorrhagic stroke patients. Regarding to a comparison between two groups, early poststroke seizures was associated with presence of hemorrhagic stroke and younger age. For the poststroke epilepsy group, there was a relation between ischemic stroke subtype, the elderly, atrial fibrillation, abnormal kidney function, and high serum calcium.

Conclusion: The incidence of poststroke seizures was found to be occur in 5.17 patients/1,000 people population/year. Ischemic stroke, older age, atrial fibrillation, kidney function, and high serum calcium found to be possible predictors for poststroke epilepsy.

Keywords: Poststroke seizure, Poststroke epilepsy, Stroke, Seizure, Epilepsy (J Thai Stroke Soc. 2020;19(2):22-30)

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อุบัติการณ์และปัจจัยเสี่ยงในการเกิดภาวะชักและโรคลมชักหลังการเกิดโรคหลอดเลือดสมอง

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บทคัดย่อ

วัตถุประสงค์ เพื่อศึกษาอุบัติการณ์ของการเกิดอาการชักที่เกิดขึ้นภายหลังการเกิดโรคหลอดเลือดสมองในระยะแรก (early poststroke seizure) และโรคลมชักที่เกิดขึ้นจากโรคหลอดเลือดสมอง (poststroke epilepsy) ในคนไทย และความแตกต่างระหว่างทั้งสองกลุ่ม รวมถึงปัจจัยเสี่ยงที่เกี่ยวข้องกับการเกิดโรคลมชักจากโรคหลอดเลือดสมอง

วิธีวิจัย การศึกษานี้เป็นการศึกษาผู้ป่วยทั้งหมดที่มีอาการชักหลังการเกิดโรคหลอดเลือดสมองที่คณะแพทยศาสตร์วชิรพยาบาล ตั้งแต่ 1 มกราคม 2557 จนถึง 31 ธันวาคม 2561 โดยผู้ป่วยจะถูกแบ่งออกเป็นสองกลุ่ม ได้แก่ กลุ่มที่มีอาการชักภายใน 7 วันหลังเกิดโรคหลอดเลือดสมอง และกลุ่มที่เกิดอาการชักหลังจาก 7 วันที่เกิดโรคหลอดเลือดสมองไปแล้วซึ่งในกลุ่มหลังนี้จะถือว่าเป็นโรคลมชักที่เกิดขึ้นจากโรคหลอดเลือดสมอง

ผลการวิจัย จากผู้ป่วยที่มาด้วยโรคหลอดเลือดสมองทั้งหมด 3600 รายที่ไม่มีประวัติของโรคลมชักมาก่อน พบว่ามีผู้ป่วย 93 คนที่เกิดอาการชักขึ้นหลังจากการเกิดโรคหลอดเลือดสมอง โดยผู้ป่วยส่วนใหญ่ 54 ราย (58.1%) อยู่ในกลุ่มโรคเลือดออกในสมอง สำหรับผู้ป่วยโรคหลอดเลือดสมองตีบพบว่ามีอาการชักทั้งสิ้น 39 ราย (41.9%) โดยมีผู้ป่วย 59 รายที่เป็นกลุ่มที่มีอาการชักภายใน 7 วันหลังเกิดโรคหลอดเลือดสมอง โดย 44 คน (74.6%) เป็นผู้ป่วยโรคเลือดออกในสมองและ 15 คน (25.4%) เป็นผู้ป่วยโรคหลอดเลือดสมองตีบ สำหรับกลุ่มโรคลมชักที่เกิดขึ้นจากโรคหลอดเลือดสมอง พบผู้ป่วยทั้งสิ้น 34 ราย โดยในจำนวนนี้ 24 ราย (70.6%) เป็นผู้ป่วยโรคหลอดเลือดสมองตีบ และ 10 ราย (29.4%) เป็นผู้ป่วยโรคเลือดออกในสมอง จากการเปรียบเทียบระหว่างสองกลุ่ม พบว่ากลุ่มที่มีอาการชักภายใน 7 วันหลังเกิดโรคหลอดเลือดสมองมีความสัมพันธ์กับโรคเลือดออกในสมองและที่อายุน้อยกว่า ส่วนกลุ่มโรคลมชักที่เกิดขึ้นจากโรคหลอดเลือดสมองมีความสัมพันธ์กับชนิดของโรคหลอดเลือดสมองตีบ, อายุ, ภาวะหัวใจเต้นผิดจังหวะชนิด atrial fibrillation, การทำงานของไตที่ผิดปกติ, และภาวะแคลเซียมในเลือดสูง

สรุป จากการศึกษานี้พบว่าอุบัติการณ์ของการเกิดอาการชักภายหลังการเกิดโรคหลอดเลือดสมองเท่ากับ 5.17 คนต่อประชากร 1,000 คนต่อปี โดยโรคหลอดเลือดสมองตีบ, อายุที่มากขึ้นภาวะหัวใจเต้นผิดจังหวะชนิด atrial fibrillation, การทำงานของไตที่ผิดปกติ, และภาวะแคลเซียมในเลือดที่สูงมีความสัมพันธ์กับการเกิดโรคลมชักที่เป็นผลจากโรคหลอดเลือดสมอง

คำสำคัญ: โรคหลอดเลือดสมอง, อาการชักจากโรคหลอดเลือดสมอง, โรคลมชักจากโรคหลอดเลือดสมอง, โรคหลอดเลือดสมองขาดเลือด, โรคหลอดเลือดออกในสมอง (J Thai Stroke Soc. 2020;19(2):22-30)

Introduction

Stroke is one of the causes of seizure and epilepsy underlying approximately 6.64% – 11% depending on the studies[1-3]. The stroke caused seizures can be divided into 2 types according to the definition of International League Against Epilepsy (ILAE) in 2014, which based on the criteria for the timing of seizures after a stroke occurrence. For the early poststroke seizures or acute symptomatic seizures, which refers to seizures that occur within 7 days after a stroke. This type of seizures is not considered epilepsy. For poststroke epilepsy, which refers to seizures that occur after 7 days after a stroke[1].

The research of Shrikant D. Pande et al. on a poststroke seizure within 7 days, in both ischemic and hemorrhagic stroke patients, it was found that the occurrence of hemorrhagic stroke, total anterior circulation stroke, low serum APTT, ischemic heart disease, using levodopa significantly affects early poststroke seizure[2].

The study of Haapaniemi et al. studied hemorrhagic stroke patients and the cause of poststroke epilepsy (occurring > 7 days after the insult), and found that cortical involvement, age, the volume of hemorrhage and early seizure also significantly affected poststroke epilepsy[4].

Previously, although, there were several studies on this issue, study results, and definitions of early poststroke seizures and poststroke epilepsy were still different from each study since there was no international standard practice for separating these two groups of symptoms. Furthermore, there has not yet been any study in Thai. Therefore, this is the beginning of this research. Its results may lead to more accurate predictions and treatment plans for stroke patients, as well as the prevention of seizures or epilepsy that may occur, to reduce disabilities, admission rate, and resources used for patient care.

Objectives

The primary objective was to study the incidence of early poststroke seizure and poststroke epilepsy

The secondary objective was to compare the differences in factors associated with early poststroke seizures and poststroke epilepsy.

Methods

Study design

This study was a retrospectively descriptive study with data comparison between early post stroke seizure and post stroke epilepsy.

Population

The population was the patients who have seizure after stroke in Vajira Hospital. he sample size determination in this study can be calculated from the formula for calculating the sample size

$$n_1 = \left[\frac{Z_{1-\alpha/2}\sqrt{\bar{p}\bar{q}\left(1+\frac{1}{r}\right)} + Z_{1-\beta}\sqrt{p_1q_1+\frac{p_2q_2}{r}}}{\Delta}\right]^2$$

The number of samples used in the group of patients should not be less than 90 people in total. This study uses a sample group of 93 people; therefore the number of samples used in this study is sufficient for analysis.

Inclusion criteria

1. All patients with seizures after the occurrence of both ischemic and hemorrhagic stroke, who admitted at the Faculty of Medicine, Vajira Hospital, Navamindradhiraj University, during 2014–2018.

2. No history of epilepsy before admission.

3. Age ≥ 15 years.

4. Followed up for a minimum of 6 months after discharge.

Exclusion criteria

1. Patients with a past or present history of central nervous system infection or tumor.

2. Patients with a history of neurosurgical procedures.

3. Patients with traumatic intracranial bleeding.

4. Patients with history of toxic or substance abuse.

Data analysis

1. Quantitative data included the number of patients with early poststroke seizure and poststroke epilepsy. This data was presented using the mean and standard deviation or median and quartile range.

2. Qualitative data included gender, age, nationality, stroke type, comorbidity, seizure symptom, results of CT brain, laboratory test, and Electroencephalogram. This data was presented by using frequency and percentage and compared by using the Chi-Square test or Fisher's exact test.

3. Data comparison was done by mean, standard deviation, proportion, or median Student's t-test.

Results

According to the study of the incidence of poststroke seizures, there was a total of 93 patients with occurred seizures from 3,600 patients with stroke, accounting for 5.17 patients/1,000 people population/year.

Table 1. *General characteristics*

Variables	**Total (n=93)**		**Early poststroke seizure (n=59)**		**Poststroke epilepsy (n=34)**		**p-value***
Gender							
Male	55	(59.1)	32	(54.2)	23	(67.6)	0.205[b]
Female	38	(40.9)	27	(45.8)	11	(32.4)	
Ages (years)	62.52±16.85		59.68±16.99		67.44±15.64		0.032[a]
Race							
Thai	92	(98.9)	58	(98.3)	34	(100)	1.000[c]
Other	1	(1.1)	1	(1.7)	0	(0.0)	
Comorbidity							
Hypertension	59	(63.4)	39	(66.1)	20	(58.8)	0.483[b]
Diabetic mellitus	27	(29.0)	15	(25.4)	12	(35.3)	0.313[b]
Dyslipidemia	23	(24.7)	14	(23.7)	9	(26.5)	0.768[b]
Ischemic heart disease	8	(8.6)	6	(10.2)	2	(5.9)	0.706[c]
Atrial fibrillation	14	(15.1)	3	(5.1)	11	(32.4)	<0.001[b]
Other comorbidity	46	(49.5)	27	(45.8)	19	(55.9)	0.347[b]

Variables	Total (n=93)		Early poststroke seizure (n=59)		Poststroke epilepsy (n=34)		p-value*
Types of cerebrovascular disease							
Ischemic stroke	39	(41.9)	15	(25.4)	24	(70.6)	<0.001[b]
Hemorrhagic stroke	54	(58.1)	44	(74.6)	10	(29.4)	
TOAST classification (n=39)							
Large-artery atherosclerosis	23	(59.0)	10	(66.7)	13	(54.2)	0.528[c]
Cardioembolism	12	(30.8)	3	(20.0)	9	(37.5)	
Small-vessel occlusion	2	(5.1)	1	(6.7)	1	(4.2)	
Stroke of other determined etiology	1	(2.6)	0	(0.0)	1	(4.2)	
Stroke of undetermined etiology	1	(2.6)	1	(6.7)	0	(0.0)	
Territories (n=39)							
TACS	4	(10.3)	1	(6.7)	3	(12.5)	1.000[c]
PACS	30	(76.9)	12	(80.0)	18	(75.0)	
POCS	4	(10.3)	2	(13.3)	2	(8.3)	
LACS	1	(2.6)	0	(0.0)	1	(4.2)	
Hemorrhagic transformation (n=39)	2	(5.1)	2	(13.3)	0	(0.0)	0.142[c]
Treatment for ischemic stroke (n=39)							
Antiplatelet	29	(76.3)	14	(100)	15	(62.5)	0.014[c]
Anticoagulant	9	(23.7)	0	(0.0)	9	(37.5)	
Thrombolysis (rtPA)		(0.00)	0	(0.0)	0	(0.0)	
Mechanical thrombectomy		(0.00)	0	(0.0)	0		
Hemorrhagic stroke (n=54)							
Epidural	1	(1.9)	1	(2.3)	0	(0.0)	1.000[c]
Subdural	10	(18.5)	3	(6.8)	7	(70.0)	<0.001[c]
Subarachnoid	21	(38.9)	19	(43.2)	2	(20.0)	0.284[c]
Intraventricular	8	(14.8)	8	(18.2)	0	(0.0)	0.362[c]
Lobar	14	(25.9)	14	(31.8)	0	(0.0)	0.048[c]
Subcortical	7	(13.0)	7	(15.9)	0	(0.0)	0.325[c]
Brainstem	1	(1.9)	1	(2.3)	0	(0.0)	1.000[c]
Cerebellum	2	(3.7)	1	(2.3)	1	(10.0)	0.339[c]
Arteriovenous malformation	1	(1.9)	1	(2.3)	0	(0.0)	1.000[c]

Data are presented as number (%) or mean±standard deviation.

**:comparison between early poststroke seizure and poststroke epilepsy; [a]Student's t-test, [b]Chi-square test, [c]Fisher's exact test*

Table 2. *Clinical characteristics*

Variables	Total (n=93)		Early poststroke seizure (n=59)		Poststroke epilepsy (n=34)		p-value*
Seizure classification							
Focal onset seizure	12	(12.9)	6	(10.2)	6	(17.6)	0.230[b]
Generalize onset seizure	24	(25.8)	13	(22.0)	11	(32.4)	
Unknown onset seizure	57	(61.3)	40	(67.8)	17	(50.0)	
Laboratory test results							
Serum glucose or CBG[α] (mg%)	160.11±97.81		158.08±95.33		163.45±103.27		0.811[a]
BUN (mg/dL)	18.32±14.03		14.59±8.39		24.88±18.93		0.005[a]
Creatinine (mg/dL)	1.11±0.93		0.93±0.63		1.43±1.25		0.014[a]
Serum sodium (mEq/L)	138.52±3.99		138.31±4.13		138.88±3.77		0.505[a]
Serum calcium (mg/dL)	8.91±0.73		8.67±0.59		9.27±0.77		<0.001[a]
Serum magnesium (mg/dL)	2.03±0.33		2.00±0.35		2.08±0.29		0.314[a]
AST (mg/dL)	40.57±28.65		44.17±23.46		36.07±33.97		0.268[a]
ALT (mg/dL)	37.84±40.71		44.03±46.93		29.89±29.91		0.170[a]
ALP (mg/dL)	109.78±83.39		99.81±86.48		122.96±78.72		0.271[a]
Electroencephalogram (EEG)							
Normal	3	(3.2)	1	(1.7)	2	(5.9)	0.057[c]
Abnormal	7	(7.5)	2	(3.4)	5	(14.7)	
Not done	83	(89.2)	56	(94.9)	27	(79.4)	

Data are presented as number (%) or mean±standard deviation.

**:comparison between early poststroke seizure and poststroke epilepsy; [a]Student's t-test, [b]Chi-square test, [c]Fisher's exact test*

[α]:capillary blood glucose

According to general characteristics of patients with seizures, the results showed that most of them are male. The poststroke epilepsy group had a longer average age. Atrial fibrillation found in poststroke epilepsy by 32.4%, which was more than the early poststroke seizure (p-value < 0.001) (Table 1).

Besides, the early poststroke seizure found to be associated with hemorrhagic stroke by 74.6%. Meanwhile, poststroke epilepsy was more common in patients with ischemic stroke by up to 70.6%. If classified by TOAST classification, patients with ischemic stroke found that most of the early poststroke seizure

group has large artery atherosclerosis 66.7%, followed by cardioembolism 20%. The mostly found area of stenosis was at partial anterior circulation by up to 80%. Most of the poststroke epilepsy group had large-artery atherosclerosis by 54.2%, followed by cardioembolism 37.5%. The mostly found area of stenosis was still at partial anterior circulation by 75%. This study found that there were only two patients with occurred hemorrhagic transformation, which were found only in the early poststroke seizure group.

Among 54 hemorrhagic stroke patients, the early poststroke seizure group found to have the highest rate of subarachnoid hemorrhage 43.2%. Meanwhile, the poststroke epilepsy group had the highest subdural hemorrhage 70% (Table 1). The clinical features of seizures in this study showed that patients in both early poststroke seizure and poststroke epilepsy had no different symptoms of seizures and Electroencephalogram results. The laboratory test results showed that the mean values of blood urea nitrogen, creatinine and serum calcium of the poststroke epilepsy patients were significantly higher than the other (Table 2).

Discussion

This study is the first study to determine the incidence of early poststroke seizure and the possible predictors for poststroke epilepsy in the Thai population regarding to International League Against Epilepsy (ILAE) definition of acute symptomatic seizure in 2010. According to this study, the factors associated with seizures, both early poststroke seizure and poststroke epilepsy, included hemorrhagic stroke and cortical involvement, which were not different from previous studies' results. Although there was a higher incidence for the early poststroke seizure found in the hemorrhagic stroke group, especially subarachnoid hemorrhage, there was a higher incidence of poststroke epilepsy in the ischemic stroke group as well, especially the anterior circulation. This finding might be explained by the pathogenesis hypothesis of acute symptomatic seizures. The seizure could be caused by transient biochemical abnormalities at a specific area, resulting in epileptiform discharges. On the other hand, for poststroke epilepsy, the seizure mechanism resulted from brain tissue affected by the stroke, causing changes that lead to a tendency to become epileptic networks, according to the hypothesis of epileptogenesis[5].

Many studies showed that the occurrence of early poststroke seizure was a risk factor of the poststroke epilepsy[4] and a complication of thrombolytic treatment[6]. However, in our study there was on patient received thrombolytic treatment and early poststroke seizure patients who had repeated seizures until developing into poststroke epilepsy; therefore, this relationship could not conclude in our study.

Stroke has associated with glutamate excitotoxicity wherein excessive activation of the NMDAR leads to an irreversible overload of calcium and neuronal death[7]. The role of calcium in the in vitro, glutamate injury-induced epileptogenesis model of stoke-induced epilepsy were not well characterized. One study indicates that the glutamate-injury induced epileptogenesis model of stroke-induced epilepsy is calcium-dependent and requires NMDA-receptor activation[8]. Anyway, further research needs to clarify the relationship between serum calcium and poststroke epilepsy.

For the significantly higher level of BUN and creatinine in the poststroke epilepsy group, there is no prior study found this relationship before. This result may be related to noncerebral disarrangements, such as acid–base disturbances, which may not be linked to the epileptogenesis from the available data so far.

The limitation of this study is that because this study is retrospective, some information's completeness is not enough to make conclusions. For example, blood tests could complete by 66.66%. Meanwhile, for the occurrence of hemorrhagic transformation, which may affect the occurrence of seizures, the study results could find less than the actual result, since the follow-up brain CT scan was not a standard protocol that can perform in all cases, as well as EEG, which can only be done by 10.7%. Besides, information on the stroke severity (NIHSS), and blood volume in a CT scan, which may be associated with seizures, were not enough to conclude the relationship.

At present, there are no standard guidelines for antiepileptic drugs to prevent poststroke seizures. Also, it found that distributing antiepileptic drugs to prevent seizures could lead to worse outcomes of treatment[9]. No studies have proven that any antiepileptic drugs can prevent both seizures and epilepsy. The current practice still applies the same approach to treat seizure or epilepsy from other causes, which generally must be considered by the seizure type and other factors, such as age, gender, comorbidity, or other current medication. However, in the long term, if there is an understanding of the mechanism of stroke caused epileptogenesis and the new invention of antiepileptic drugs that respond to the prevention of epileptogenesis, there will be medication to prevent the occurrence of poststroke epilepsy in the future.

Conclusion

The incidence of poststroke seizures in this study found to occur in 5.17 patients/1,000 people population/year. Poststroke seizure and poststroke epilepsy are common causes of hospital admissions, either as a presenting feature or as a complication after a stroke. Stroke types, older age, atrial fibrillation, abnormal kidney function, and high serum calcium are possible predictors for poststroke epilepsy.

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