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Early Seizures After Stroke: Neurology Intensive Care Unit Experience

İnme Sonrası Erken Başlangıçlı Nöbetler: Nöroloji Yoğun Bakım Ünitesi Deneyimi

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Abstract

Objective: The aim of this study was to investigate the frequency of early seizures, the affecting factors, and the prognostic effect of seizures in patients with acute ischemic stroke (AIS), intracerebral hemorrhage (ICH), and sinus venous thrombosis (SVT) examined in the intensive care unit (ICU).

Materials and Methods: In the neurology ICU, the records of patients followed up with AIS, ICH, and SVT within a defined time period were retrospectively examined.

Results: Early seizures occurred in 48 out of 199 patients who were followed up with AIS, ICH, and SVT in the neurology ICU within the specified time period. The frequency of having early seizures was found to be higher in patients with left hemisphere lesions, cortical lesions, and those with AIS with hemorrhagic transformation. Lesion volume was found to be higher in patients with AIS who had early seizures compared with those who had AIS without seizures. Early seizures were observed in all patients with SVT who were followed up in the ICU.

Conclusion: Early seizures are a common complication in patients with stroke followed up in neurology ICUs. Determination of effective factors in early seizures is important for its early diagnosis and treatment.

Keywords: Early seizure, stroke, neurological intensive care unit

Öz

Amaç: Bu çalışmanın amacı akut iskemik inme (Aİİ), intraserebral hemoraji (İSH) ve sinüs ven trombozu (SVT) nedeni ile yoğun bakım ünitesinde (YBÜ) takip edilen hastalarda erken başlangıçlı nöbet geçirme sıklığını, bunda etkili faktörleri ve nöbetin prognoza etkisini araştırmaktır.

Gereç ve Yöntem: Nöroloji YBÜ'de, belirlenen zaman dilimi içerisinde Aİİ, İSH ve SVT tanısı ile takip edilen hasta kayıtları retrospektif olarak incelenmiştir.

Bulgular: Belirlenen zaman dilimi içinde nöroloji YBÜ'de Aİİ, İSH ve SVT tanısı ile takip edilen 199 hastadan 48'inde erken başlangıçlı nöbet ortaya çıkmıştır. erken başlangıçlı nöbet geçirme sıklığı sol hemisfer lezyonu, kortikal lezyon ve hemorajik transformasyonu olan Aİİ'li hastalarda daha yüksek bulunmuştur. erken başlangıçlı nöbet geçiren Aİİ'li hastalarda lezyon volümü nöbeti olmayan Aİİ'li hastalara göre yüksek bulunmuştur. YBÜ'de takip edilen SVT'li bireylerin tamamında erken başlangıçlı nöbet gözlemlenmiştir.

Sonuç: Nöroloji YBÜ'de takip edilen inme hastalarında erken başlangıçlı nöbet sık görülen bir komplikasyondur. Erken başlangıçlı nöbetde etkili faktörlerin tespiti erken tanı ve tedavi için önemlidir.

Anahtar Kelimeler: Erken başlangıçlı nöbet, inme, nöroloji yoğun bakım ünitesi

Introduction

Stroke is defined by the World Health Organization as a clinical syndrome characterized by the rapid onset of signs and symptoms of loss of focal cerebral function due to vascular causes (1). Strokes were divided into three main groups as cerebral ischemia (60-80%), intracerebral hemorrhage (ICH) (10-15%), and subarachnoid hemorrhage (SAH) (3-10%) based on neuroradiologic, cardiologic, hematologic, and biochemical examinations (2). Sinus venous thrombosis (SVT), which is responsible for approximately 1% of all strokes, is a neurologic emergency situation characterized by thrombosis of the intracranial cerebral sinuses and/or cerebral venous pathways leading to venous drainage retention, intracranial pressure elevation, and/or venous infarctions (3).

Seizures are well-known and serious complications of stroke (4,5,6). Post-stroke seizures can be divided into two groups

as early- and late-onset seizures according to the temporal relationship between the time of stroke and seizure. Early seizures are classified as seizures within 15 days after stroke, whereas late seizures are classified as seizures starting 16 days after stroke (7). The incidence of early or late seizures after acute ischemic stroke (AIS) has been reported in a wide range (2-67%). This ratio is between 8-15% after ICH and SAH (8,9,10). It reaches a high figure of 44% in SVT (11). The observation of early seizures in particular after stroke has been linked to many factors including type, location, size, and severity of stroke (5,6).

In this study, we investigated the frequency of early seizure development and factors affecting seizure development, the effect of seizure on disease prognosis, and its response to antiepileptic treatment in patients followed up with AIS, ICH, and SVT in the neurology intensive care unit (ICU).

Materials and Methods

One hundred ninety-nine patients who were followed up with AIS, ICH, and SVT diagnoses in the neurological ICU between January 2012 and July 2016 and met the specified inclusion criteria were included in the study. Demographic, clinical, biochemical, and neuroradiologic data of patients were obtained by investigating patient files retrospectively. Post-stroke early seizure was defined as a seizure within the first 15 days after stroke. Patients were divided into two groups as patients with and without early seizure. In the group of patients with early seizure, those with infection, metabolic disorder, and electrolyte imbalance, and drug and alcohol users were excluded from the study. Patients who had previously had epileptic seizures or were under suspicion of having seizures were excluded from both groups. Patients aged younger than 18 years with SAH, and subdural and epidural hemorrhage were excluded from the study. Clinical characteristics, radiologic findings, treatments, mean duration of hospitalization, and onset-time of seizure were recorded for each patient. Stroke types in patients were identified by considering the clinical features and neuroradiologic findings of the patients. National Institutes of Health Stroke Scale (NIHSS) scores and modified Rankin Score (mRS) were calculated from the referral neurologic examinations of patients with AIS and ICH. The information in the patient files was used to calculate the mRS three months after admission to the hospital. Patients with SVT were assessed on the basis of the functional status Barthel index (BI): poor recovery (BI 12), partial recovery (BI 13-19), and complete recovery (BI 20). Lesion volumes were calculated using diffusion-weighted magnetic resonance images (MRI) and brain computed tomography images performed within the first 24 hours after stroke during admission for patients with AIS and ICH, respectively. When lesion volumes were calculated, the relevant regions were measured by marking the circumference of the lesion area for each incision. SVT diagnosis was confirmed by using cranial MRI and MRI venography in all patients diagnosed with SVT.

Statistical Analysis

Number and percentage distributions were given to variables used in the study and categorical variables such as sex, presence of seizure, type of disease, initial symptom, lesion side, presence of status epilepticus, the number of anti-epileptic drugs (AED),

presence of hemorrhagic infarcts, type of AED, lesion size, response to treatment, and presence of cortical lesion. The mean, standard deviation, minimum and maximum values of the age, length of hospitalization, epileptic seizure duration, mRS at admission, mRS 3 months after admission, NIHSS at admission, and lesion volume variables are given. The normal distribution of continuous variables included in the study was evaluated using the Shapiro-Wilk test. Nonparametric tests were applied to variables that were not normally distributed and the median and interquartile range values are given in addition to the descriptive statistics. The lesion side, presence of cortical lesion, presence of status epilepticus, hemorrhagic infarct, and AED number on the basis of early seizures presence was statistically differentiated using the Chi-square comparison test. Likewise, the effect of status epilepticus on the lesion side in patients with seizures was analyzed using the Chi-square comparison test. The Mann-Whitney U non-parametric test was used to determine whether there was a statistically significant difference in lesion volume in terms of the presence of status epilepticus in patients with early seizures. Similarly, the Mann-Whitney U nonparametric test was used to determine whether the age, lesion volume, seizure duration, and length of stay of the individuals with early seizures were statistically significant. The chi-square comparison test was used to determine whether disease types differed statistically in terms of having early seizures. The Kruskal-Wallis nonparametric test was employed to analyze whether there was a statistically significant difference between seizure duration and lesion volume in the case of stroke type. The Mann-Whitney U non-parametric test was used to determine whether the NIHSS, lesion volume, mRS on referral, and mRS in the third month were statistically significantly different in individuals with AIS and ICH (separately) in terms of the presence of seizure. The IBM SPSS Statistics package 21.0 (IBM Corp. released 2012. IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY: IBM Corp.) and MS-Excel 2007 were used for statistical analysis and calculations. The level of statistical significance was accepted as p<0.05.

Results

The demographic information of patients included in the study is given in Table 1.

Table 1. Demographic information	
Demographic information	Number (percentage); n (%)
Sex	
Female	111 (55.8)
Male	88 (44.2)
Seizure	
Present	48 (24.1)
Absent	151 (75.9)
Stroke type	
Acute ischemic stroke	149 (74.9)
Intracerebral hemorrhage	39 (19.6)
Sinus venous thrombosis	11 (5.5)

Table 1. Continued	
Demographic information	Number (percentage); n (%)
Initial symptom	
Consciousness impairment	92 (46.2)
Hemiparesis	79 (39.8)
Speech impairment	10 (5.0)
Imbalance	7 (3.5)
Seizure	9 (4.5)
Headache	2 (1.0)
Lesion side	
Right	92 (46.2)
Left	98 (49.2)
Bilateral	5 (2.6)
Intraventricular	4 (2.0)
Status epilepticus	
Present	37 (77.1)
Absent	11 (22.9)
Seizure type	
Focal	8 (16.7)
Generalized	40 (83.3)
Anti-epileptic drug number	
Monotherapy	40 (83.3)
Polytherapy	8 (16.7)
Hemorrhagic infarct	
Present	16 (9.4)
Absent	154 (90.6)
Anti-epileptic drug type	
Phenytoin	20 (41.7)
Valproic acid	4 (8.3)
Levetiracetam	16 (33.3)
Combination	8 (16.7)
Treatment response	
Complete recovery	43 (89.6)
Partial recovery	5 (10.4)
Cortical lesion	
Present	73 (36.9)
Absent	125 (63.1)

It was found that there was no statistically significant difference between sex and having early seizures (p=0.282). Among individuals who had early seizures, right-sided lesions were found in 29.2%, left-sided lesions in 56.2%, bilateral lesions in 8.4%, and the intraventricular lesions in 6.2%. Among individuals who had no early seizures, 51.6% had right-sided lesions, 47.0% had left-sided lesions, and the remainder had bilateral and intraventricular lesions. The lesion sides showed

a statistically significant difference according to the presence of early seizure (p<0.001). The lesion side of the majority of individuals with early seizures was found as the left side, the majority of individuals with no seizures had right-sided lesion. The number of patients with early seizures and cortical lesions was calculated as 27, and the number of patients with early seizures without cortical lesions was 20. Most patients who had no early seizures had no cortical lesions. There was a statistically significant relationship between the presence of cortical lesions and individuals having early seizures (p=0.001). Most individuals with early seizures had cortical lesions, and the majority of individuals with no seizures had no cortical lesions.

Of the individuals who had early seizures, 77.1% had status epilepticus; 59.45% of the patients with status epilepticus were female, and 40.55% were male. The mean age of the patients with status epilepticus was 64±20.21 and the mean duration of hospitalization was 33.21±48.91 days. Of these patients, 62% were followed by AIS, 21.62% by ICH, and 16.22% by SVT. The lesion side was right in 27.03% of patients with status epilepticus, left in 54.05%, bilateral in 10.81%, and intraventricular in 8.11%; 16.22% of these patients had hemorrhagic infarction, 83.78% had no hemorrhagic infarction, 54.05% had cortical lesions, and 45.95% no cortical lesions. Seizure type was generalized in 86.49% and 13.54% had focal seizures.

Among the patients who had early seizures, eight had hemorrhagic infarction and 40 had none. In contrast, among the patients who had no early seizures, 8 had hemorrhagic infarction and 114 had none. The presence or absence of hemorrhagic infarction based on having early seizure was statistically significant (p=0.042). The majority of individuals who had early seizures had no hemorrhagic infarction. Forty patients with early seizures had only one AED and 8 had more than one AED (Table 2).

The mean age of the patients who had early seizures was 67.06±19.42 years, and the mean age of those who had no seizures was 73.76±12.16 years. The mean age of patients showed no statistically significant difference in terms of the presence of early seizures (p=0.076). The mean hospitalization duration of patients who had early seizures was determined as 28.66±43.84 days and that of patients who had no seizures was 34.32±43.49 days. There was no statistically significant difference in the length of hospitalization for patients in terms of presence or absence of early seizures (p=0.486). The mean seizure duration of patients who had early seizures was calculated as 2.04±2.57 day. The mean lesion volume was calculated as 90.50±96.45 cm^3 for the patients who had early seizures, and the mean lesion volume for those with no seizures was 69.79±104.72 cm^3. There was a statistically significant difference in lesion volume values between patients with and without early seizures (p=0.033). The lesion volumes of patients with early seizures were higher compared with those without seizure (Table 3).

Eight patients with AIS had early seizures and 120 had no early seizures, 8 of the patients with ICH had early seizures and 31 had no early seizures, and 11 patients with SVT (all those with SVT) had early seizures (Table 4). The mean duration of seizure for individuals with AIS was 2.55±2.84 days, the mean duration of seizure for those with ICH was 2.12±2.41 days, and the mean duration of seizure for patients with SVT was 0.63±1.20 days. There was no statistically significant difference in seizure duration

Table 2. Comparison of sex, lesion side, presence of cortical lesion, presence of status epilepticus, and presence of hemorrhagic infarct based on early seizure

Variables	Early seizure		Test statistic	
	Present n (%)	Absent n (%)	χ2	p
Sex				
Female	30 (62.5)	81 (53.6)	1.159	0.282
Male	18 (37.5)	70 (46.4)		
Lesion side				
Right	14 (29.2)	78 (51.6)		
Left	27 (56.2)	71 (47.0)	18.802	<0.001
Bilateral	4 (8.4)	1 (0.7)		
Intraventricular	3 (6.2)	1 (0.7)		
Cortical lesion				
Present	27 (57.4)	46 (30.5)	11.212	0.001
Absent	20 (42.6)	105 (69.5)		
Status epilepticus				
Present	37 (77.1)	-		
Absent	11 (22.9)	-	-	-
Hemorrhagic infarct				
Present	8 (16.7)	8 (6.6)	4.129	0.042
Absent	40 (83.3)	114 (93.4)		
Anti-epileptic drug number				
Monotherapy	40 (83.3)	-		
Polytherapy	8 (16.7)	-	-	-

in terms of stroke type (p=0.094). The mean lesion volume for individuals with AIS and ICH was calculated as 80.26±111.32 cm³ and 48.89±59.40 cm³, respectively. There was no statistically significant difference in lesion volumes in terms of stroke types (p=0.935).

The average NIHSS scores of individuals with AIS with and without early seizures were calculated as 17.89±9.10 and 20.43 ±8.47, respectively. The mean lesion volume for individuals with AIS who had early seizures was 102.60±104.89 cm³, and 75.24±112.52 cm³ for those without seizures. NIHSS values showed no statistically significant differences according to the presence of seizures (p=0.230). However, lesion volumes were statistically significantly different in terms of the presence of seizures (p=0.034); the lesion volumes of patients with AIS who had early seizures were higher than those without seizures. The average NIHSS scores of patients with ICH who had early seizures were calculated as 22.75±8.56, and 23.87±8.48 for those without seizures. The mean lesion volume was determined as 49.65±43.02 cm³ for individuals with ICH who had early seizures, and 48.70±63.54 cm³ for those without seizures. There was no statistically significant difference between NIHSS and lesion volume values based on the presence of early seizures (p=0.848, p=0.676, respectively) (Table 5).

Discussion

In this study, we investigated the frequency of early seizure development and factors affecting seizure development, the effect of seizure on prognosis, and the response to antiepileptic treatment in patients with AIS, ICH, and SVT who were followed up in the neurology ICU. It was found that the presence of left hemispheric lesions, cortical lesions, presence of hemorrhagic infarct, and lesion size increased the frequency of having early seizures.

Table 3. Comparison of age, hospitalization time, seizure-onset time, and lesion volume based on early seizure

Variables	Early seizure		Test statistic	
	Presence Mean ± SD Median (IQR)	Absent Mean ± SD Median (IQR)	Z	p
Age	67.06±19.42 72.50 (27.00)	73.76±12.16 75.00 (15.00)	1.772	0.076
Hospitalization time	28.66±43.84 12.00 (19.00)	34.32±43.49 18.00 (35.00)	0.697	0.486
Seizure-onset time	2.04±2.57 1.00 (3.00)	-	-	-
Lesion volume	90.50±96.45 60.51 (129.25)	69.79±104.72 27.16 (78.80)	2.131	0.033
SD: Standard deviation, IQR: Interquartile range				

Table 4. Comparison of stroke type based on early seizures

Variables	Stroke type			Test statistic	
Early seizure	AIS n (%)	ICH n (%)	CVT n (%)	χ2	p
Presence	29 (19.5)	8 (20.5)	11 (100.0)	36.647	<0.001
Absent	120 (80.5)	31 (79.5)	0 (0.0)		
AIS: Acute ischemic stroke, ICH: Intracerebral hemorrhage, CVT: Cerebral venous thrombosis					

Although post-stroke seizures have been known for many years, many questions remain unanswered regarding this subject. Furthermore, many studies on this subject have shown different results (12,13). However, the most common cause of seizures seen in older people is stroke. Post-stroke seizure rates in three different studies were reported at 9%, 14%, and 19%, respectively. In another study, it was found that 3.2% of patients followed for seven years after stroke had developed epilepsy (10,14,15,16,17,18). We also investigated the frequency of early seizures and affecting factors in patients with AIS, ICH, and SVT in our neurology ICU. Of the patients followed up within the defined period, 19.5% of those with AIS, 20.5% of patients with ICH, and 100% of patients with SVT had early seizures; 16.7% of these seizures were focal (partial) and 83.3% were generalized. Previous studies have shown different rates for post-stroke early seizures including 35%, 48%, and 54% (10,19,20,21). In our study, this rate was 24.1% in patients in the ICU. Patients with AIS and ICH did not differ in terms of post-stroke early seizure incidence; however, all of the patients with SVT followed-up experienced early seizures after stroke; 72.7% (n=8) of these patients had seizure during admission. Additionally, the mean duration of seizures in patients with SVT was shorter than in those patients with AIS and ICH. This suggests seizure presence in patients with SVT is an indication for follow-up in the ICU. Bladin et al. (22) found that ICH was an independent risk factor for post-stroke seizure in their study conducted on large number of patients. The different results found in our study may be due to the smaller number of patients. Kammersgaard and Olsen (15) found that being young carried a risk for the development of seizures after stroke. In some studies conducted in this regard, age was found not to be an independent risk factor in post-stroke seizure (10,23). In our study, we also found no differences in patients' age with respect to those with and without post-stroke early seizures. Different results have also been obtained in studies that investigated whether sex was a risk factor in the development of seizures after ischemia (10,15,20,23). In our study, we found that sex was not effective in the development of early seizures after ischemia.

In studies that investigated risk factors for post-stroke seizures, the best-known risk factor for early seizures after AIS was cortical involvement (10,22). In our study, we found that cortical involvement in patients with AIS and ICH had a significant effect on early seizure formation.

In our study, we found that if hemorrhagic transformation was present in patients with AIS, the rate of early seizure was higher in this patient group compared with the non-hemorrhagic group. Previous studies found cardioembolic events as the cause of this and the increased risk of post-stroke seizure in patients with AIS (22,24,25). If cardioembolic infarcts are thought to have a high risk of hemorrhagic transformation, our findings may be related to this.

Another result of our study was that the lesion volume was significantly larger in patients with AIS who had early seizures relative to patients with AIS who had no seizures. However, there was no relationship between the presence of early seizure and lesion size in patients with ICH. In a study conducted by Bladin et al., (22) it was found that the lesion size was an independent risk factor for AIS without experiencing post-stroke seizures, consistent with our study, whereas there was no correlation between lesion size and seizure in ICH. The cause of early seizures after AIS is thought to be the formation of an electrically irritable tissue as a result of cellular biochemical dysfunction. It is thought that the increase of extracellular glutamate is also effective in this. It has been observed that depolarization of the area surrounding the infarct increases. There is also a relationship between infarct volume in the ischemic area and the severity and number of depolarizing events. These findings in the literature are consistent with the results of our study in which we found that infarct volume increased the rate of early seizure development in patients with AIS (13,26,27,28). The mechanisms leading to early seizure in ICH have not yet been elucidated (22).

One of the interesting findings of our study was that patients with left hemisphere lesions had a higher risk of developing early seizures compared with patients with right hemisphere lesions. We found no information in the related literature regarding whether the hemispheric variable increased the risk of post-stroke seizures. The reason for this may be due to the pathophysiologic mechanisms leading to early seizures after ischemia. In other words, cellular biochemical dysfunction may facilitate different biochemical and histologic contents of the left hemisphere. For example, in a study, the amount of iron in the left hemisphere was found to be

Table 5. Comparison of National Institutes of Health Stroke Scale and lesion volume values based on early seizure in patients with AIS and ICH

| Variables | Early seizure | | Test statistic | |
	Present Mean ± SD Median (IQR)	Absent Mean ± SD Median (IQR)	Z	p
NIHSS (AIS)	17.89±9.10 16.00 (19.50)	20.43±8.47 23.00 (13.00)	1.200	0.230
Lesion volume (AIS)	102.60±104.89 70.38 (150.74)	75.24±112.52 25.31 (99.55)	2.116	0.034
NIHSS (ICH)	22.75±8.56 28.00 (16.50)	23.87±8.48 25.00 (11.00)	0.192	0.848
Lesion volume (ICH)	49.65±43.02 37.85 (66.20)	48.70±63.54 33.45 (52.44)	0.417	0.676

NIHSS: National Institutes of Health Stroke Scale, SD: Standard deviation, IQR: Interquartile range, AIS: Acute ischemic stroke, ICH: Intracerebral hemorrhage

higher than in the right hemisphere, which was thought to lead to more oxidative stress and mitochondrial dysfunction in the left hemisphere (29).

One of the findings of our study was that 54.5% (n=6) of patients with SVT had lesions in the superior sagittal sinus. This is consistent with the study conducted by Jacobs et al. (30). In their study, the superior sagittal sinus and cortical venous thrombosis, which provides venous drainage from the motor and sensorial cortex, were found to be a risk for seizures in SVT.

The retrospective nature of our research and the lack of electroencephalography records are limitations to our study. However, our study is important and valuable because it is the first study to evaluate patients with AIS, ICH and SVT who were followed up in the ICU and had early seizures.

Ethics

Ethics Committee Approval: Retrospective study.
Informed Consent: Retrospective study.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ş.G., G.V., Concept: Ş.G., G.V., Design: Ş.G., Data Collection or Processing: Ş.G., G.V., Analysis or Interpretation: Ş.G., G.V., Literature Search: G.V., Writing: Ş.G., G.V.

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