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Evaluation of Seizure After Stroke in Stroke Unit

İnme Merkezinde İnme Sonrası Nöbetin Değerlendirilmesi

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Abstract

Objective: Patients with stroke may experience epileptic seizures as acute phase (usually defined as the first 15 days) or late phase complications. Risk factors are young age, male sex, cortical involvement and hemorrhagic transformation. Our aim was to investigate the etiologic factors and to determine the high-risk groups for the 1 year seizure rate of patients who are followed up in our clinic with a diagnosis of acute ischemic stroke.

Materials and Methods: This study was included in a retrospective review of 299 patients who underwent regular out-patient clinic visits for 1 year followed by a diagnosis of acute ischemic stroke in the Department of Neurology at the Eskisehir Osmangazi University Faculty of Medicine between January 1st, 2012, and January 1st, 2015.

Results: We found that thrombolytic therapy in patients with ischemic stroke decreased post-stroke seizure (p=0.043), whereas decompressive craniectomy (p=0.048), endovascular treatment (p=0.032), and cortical involvement (p=0.003) increased post-stroke seizures.

Conclusion: According to our study, patients with cortical involvement, modified Rankin Scale score 4 and 5 at discharge, presence of major vascular occlusion treated with endovascular treatment, and those with decompressive craniectomy were high-risk groups. Prospective observational drug trials can be performed because double-blind placebo drug studies are not possible in high-risk groups.

Keywords: Ischemic stroke, seizure after stroke, prophylactic antiepileptic treatment

Öz

Amaç: İnmenin akut veya geç döneminde epileptik nöbetler görülebilir. Risk faktörleri genç yaş, erkek cinsiyet ve hemorajik transformasyon olarak saptanmıştır. Amacımız akut iskemik inme tanısı ile kliniğimizde takip edilen hastaların 1 yıllık nöbet geçirme oranını, etiyolojik faktörlerini araştırmak ve yüksek riskli grupları belirlemektir.

Gereç ve Yöntem: Bu çalışmaya 01.01.2012 ile 01.01.2015 tarihleri arasında Eskişehir Osmangazi Üniversitesi Tıp Fakültesi, Nöroloji Anabilim Dalı'nda akut iskemik inme tanısı ile takip edilen ve 1 sene boyunca düzenli poliklinik kontrolleri gerçekleşmiş 299 hasta retrospektif olarak taranarak dahil edilmiştir.

Bulgular: Çalışmamızda iskemik inmeli hastalarda trombolitik tedavinin inme sonrası nöbeti azalttığı (p=0,043), dekompresif kranyektomi (p=0,048) ve endovasküler tedavinin (p=0,032) ve kortikal tutulumun (p=0,003) inme sonrası nöbeti artırdığı bulunmuştur.

Sonuç: Çalışmamıza göre kortikal tutulum varlığı, taburculuk modifiye Rankin Skalası skoru 4 ve 5 olması, endovasküler tedavi uygulanan majör damar oklüzyonu varlığı ve dekompresif kranyektomi yapılmış olması yüksek riskli grubu oluşturmaktadır. Yüksek riskli gruplarda çift kör plasebo ilaç çalışması yapılması mümkün olmadığından prospektif gözlemsel ilaç çalışmaları yapılabilir.

Anahtar Kelimeler: İskemik inme, inme sonrası nöbet, profilaktik antiepileptik tedavi

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Introduction

Epileptic seizure may occur in patients with stroke in the acute phase (usually defined as 15 days following a stroke) or in the chronic phase (1). The frequency of seizures following stroke is 4.6-11.5% (2,3,4). The risk factors are young age, male sex, cortical involvement, and hemorrhagic transformation (5,6). The occurrence of seizures in the late phase or development of epilepsy can worsen the prognosis of patients with stroke (7). Today, there is no consensus about the use of prophylactic antiepileptic treatment in patients who had an ischemic cerebrovascular accident.

It is important to know which factors cause seizures to take precautions. Different studies report different post-stroke seizure incidences but insufficient studies have investigated the relationship between decompressive craniectomy, intravenous (IV) tissues plasminogen activator (r-tPA), endovascular treatment, and post-stroke seizures. In light of these data, our aim was to investigate the frequency of seizures in a 1-year period and etiologic factors and to determine which patients with stroke had the highest risk among those who were followed up by our clinic.

Materials and Methods

This study was performed to investigate the risk factors of post-stroke seizures and to determine which patients were at the highest risk among those who admitted to the emergency service of Eskisehir Osmangazi University within 24 hours following the initiation of symptoms, and who were then followed up by our clinic. The medical records of 299 patients with acute stroke who were admitted to the neurology department of Eskisehir Osmangazi University in between January 1st, 2012, and January 1st, 2015, were retrospectively screened and these patients were included in the study.

The inclusion criteria were the followings: Admitting to the emergency service of Eskisehir Osmangazi University in 24 hours following focal neurologic deficit, being diagnosed as having acute ischemic stroke after performing neuroimaging, detected etiologic factor for the stroke and being followed regularly by the clinic of neurology of Eskisehir Osmangazi University for 1 year following stroke. High levels of urea-creatinine, renal or hepatic pathologies, diagnosis of epilepsy prior to stroke, using antiepileptic drugs (AEDs) prior to stroke, malignancy, expectancy of life shorter than 1 year, not being followed up in another study, a concomitant psychiatric disease, and current use of drugs that shorten the epileptic threshold were the exclusion criteria. The study was approved by the Ethics Committee of Eskisehir Osmangazi University, Faculty of Medicine on September 29th, 2014 (8058721/353). Patient approval is not necessary because it is a retrospective study.

All patients were examined by a neurologist and were hospitalized after the consideration of the initial cranial computed tomography (CT) and appropriate treatment was initiated. Then, to search for the etiology; carotid Doppler ultrasonography, control cranial CT, echocardiogram (ECHO), electrocardiogram, 24-hour rhythm holter, and if necessary, cerebral-neck CT angiography, magnetic resonance imaging, and MR angiography were performed. Data including age, sex, symptom initiation time, way of coming to the emergency room and transportation time, performing time of cerebral imaging, eligibility for thrombolytic treatment, whether IV-tPA was performed, whether endovascular treatment was performed, medical history (prior stroke, prior transient ischemic attack, diabetes mellitus, hypertension, coronary artery disease, cardiac failure, cardiac valvular disease, atrial fibrillation, malignancy, diagnosis of malignancy within the 1-year follow-up, whether the patient underwent decompressive craniectomy, whether the patient received prophylactic antiepileptic treatment, whether the patient had liver or kidney failure, and medication use), modified Rankin Score (mRS) at admission, hemorrhagic transformation in neuroimaging were recorded in the hospital's registry and patients' epicrisis. The patients were screened with the "G46" code in the hospital's registry. The search resulted in 1068 patients and 299 were included in the study according to the inclusion and exclusion criteria. Data including whether the patient had a seizure, etiology of stroke, the frequency of seizures if the patient had seizures, AED use, drugs used that may affect seizure threshold, and mRS scores at the end of the first year were gathered from the registry. The patients were categorized according to whether they were given IV r-tPA. Patients with no contraindications and aged 18-80 years, who were admitted with acute ischemic stroke within 4.5 hours, whose Alberta Stroke Program Early CT (ASPECT) score was 4 or higher and National Institutes of Health Stroke Scale (NIHSS) score was 4 or higher were given IV r-tPA. Patients with ASPECT scores higher than 6 and with NIHSS scores higher than 6 who were admitted after the first 4.5 hours after symptom onset, patients with large vessel occlusion in whom thrombolytic treatment was contraindicated and those with large vessel occlusion in whom thrombolytic treatment failed, were given endovascular treatment. Recanalization degrees were defined using a cerebral infarction grading system, the thrombolysis in cerebral infarction (TICI) scale; grade 0 = no recanalization, grade 1 and 2a = partial recanalization, and grade 2b and 3 = fully recanalization. Urgent decompressive surgery was performed in patients who developed intracerebral herniation during follow-up; they were subsequently followed-up in the neurology clinic. The patients were later called back for follow-up 1 month after discharge and mRS scores were recorded either through direct examination or via the telephone.

Statistical Analysis

Clinical, demographic, and radiologic features of the patients with acute ischemic stroke were compared. The IBM SPSS Statistics 21 pocket program was used for analysis. N, average, and standard deviation were used for continuous variables that were distributed normally, and the t-test was used for independent samples. Median, 25th and 75th percentiles were used for variables that were not distributed normally and the Mann-Whitney U test was used for analysis. For categorical variables, percentiles were used and the chi-square test was used for analysis. The significance level was set at $p<0.05$.

Results

Of the 299 patients, 50 (16.7%) had seizures in the first year. Of 50 patients, 24 (8%) had early seizures (within 15 days

following stroke), 38 (12.7%) had late seizures, and 12 had both early and late seizures.

Of 92 patients who were treated with IV r-tPA, 8 had seizures (Table 1).

There were no differences between patients who were and were not treated with IV r-tPA in terms of age (p=0.375), sex (p=0.704), decompressive craniectomy (p=0.999), hemorrhagic transformation (p=0.154), endovascular treatment (p=0.104), prophylactic AED use (p=0.380), and cortical involvement (p=0.708). Patients who were treated with thrombolytic treatment had less seizures compared with patients who were not treated (p=0.043), and patients who were treated with thrombolytic treatment had higher mRS scores at admission (p=0.008) and lower mRS scores at discharge (p>0.001) (Table 2).

Twenty-five (21.9%) of 114 patients with large vessel occlusion, and 23 (14.7%) of 156 patients with cardioembolism had seizures. None of 21 patients with small vessel disease had seizures. Other etiologic factors were systemic lupus erythematosus and neuro-Behçet disease, and 2 (50%) of these had seizures. None of the patients with stroke of unknown etiology had seizures. There was a statistically significant relation between etiology of stroke and seizure frequency in one year (p=0.028).

Of 212 patients with cortical involvement, 44 (20.7%) had seizures. Of the patients who had seizures, 88% had cortical involvement. The relation between seizures and cortical involvement was statistically significant (p=0.003) (Table 1).

Thirteen (4.3%) patients had decompressive craniectomy and 5 (38.5%) had seizures. There was a statistically significant relation between decompressive craniectomy and post-stroke seizures (p=0.048) (Table 1).

Of the 299 patients, 52 had hemorrhagic transformation. Of all hemorrhagic transformations, 23 (44%) had type 1 petechial hemorrhage, 16 (30%) had type 2 petechial hemorrhage, 3 (5%) had parenchymal hematoma type 1, and 10 (19%) had parenchymal hematoma type 2. Of 52 patients with hemorrhagic transformation, 13 (25%) had seizures. There was no statistically significant relation between hemorrhagic transformation and seizures (p=0.10) (Table 1).

Of the 299 patients, 31 (10.3%) were treated with prophylactic AEDs. Three (9.7%) of the patients who were treated with prophylactic AEDs had seizures. There was no statistically significant relation between treatment with prophylactic AEDs and seizures (p=0.392) (Table 1).

Patients were classified according to mRS scores on admission to the hospital, at discharge, and the end of the first year. Favorable outcomes were defined as mRS scores of 0-2 and unfavorable outcomes were defined as mRS scores of 3-5. There were statistically significant differences between epileptic seizures and the mRS scores of patients on admission to the hospital (p=0.004), at discharge (p>0.001), and at the end of the first year (p>0.001) (Table 1).

Endovascular treatment was performed in 28 patients. Nine (32%) of 28 patients had seizures. There was a statistically significant relation between endovascular treatment and seizures (p=0.032) (Table 1). The average time interval between symptom onset and needle time was 307.6 minutes in patients who were treated with endovascular treatment. Total recanalization was achieved in 14 and partial recanalization was achieved in 8 of 28 patients; recanalization was not achieved in 6 patients. There was no statistically significant relation between recanalization degrees and seizures (p=0.853). Of 28 patients who were treated with endovascular treatment, 13 had large vessel occlusion and 14 had cardioembolism; no etiology could be found in 1 patient. There was no statistically significant relation between etiology and seizures in patients who were treated with endovascular treatment (p=0.445).

Discussion

The importance of cerebrovascular diseases as an etiologic factor for late-onset epilepsy and seizures has been shown in various studies before (8). In our study, we found that IV r-tPA

Table 1. Post-stroke seizures and risk factors

Seizures	OR	95% Confidence interval	p
Age	0.928	0.503-1.712	0.934
Sex	1.264	0.684-2.336	0.94
Thrombolytic treatment	0.431	0.20-0.920	0.043
Decompressive craniectomy	3.37	1.047-10.697	0.048
Hemorrhagic transformation	1.892	0.922-3.881	0.10
Endovascular treatment	2.657	1.125-6.279	0.032
mRS at admission	0.309	0.139-0.686	0.004
mRS at discharge	0.188	0.094-0.378	>0.001
mRS at first year	0.108	0.05-0.220	>0.001
Prophylactic drug use	0.504	0.147-1.726	0.392
Cortical involvement	3.869	1.586-9.441	0.003

mRS: modified Rankin Score, OR: Odds ratio

Table 2. Variables between patients who were and were not treated with thrombolytic treatment

Thrombolytic treatment	OR	95% Confidence interval	p
Age	1.25	0.763-2.047	0.375
Sex	1.101	0.670-1.810	0.704
Seizure	0.431	0.200-0.929	0.043
Decompressive craniectomy	0.984	0.295-3.280	1
Hemorrhagic transformation	1.64	0.887-3.055	0.154
Endovascular treatment	2.069	0.942-4.547	0.104
mRS at admission	0.478	0.275-0.832	0.008
mRS at discharge	2.883	1.691-4.916	>0.001
mRS at first year	2.189	1.101-4.742	0.064
Prophylactic AED use	0.617	0.256-1.488	0.380
Cortical involvement	0.904	0.534-1.531	0.708

mRS: modified Rankin Score, AED: Antiepileptic drug, OR: Odds ratio

decreased post-stroke seizures, whereas post-stroke seizures were more frequent in patients in whom decompressive craniectomy or endovascular treatment were performed. Some *in vitro* studies showed that IV r-tPA was neurotoxic and epileptogenicity of IV r-tPA was shown in animal models (9,10,11,12). Epileptic seizures were reported following use of thrombolytic drugs in clinical trials (13,14,15). Another study on this topic showed that IV r-tPA might partially avoid late-onset seizures, possibly by causing reperfusion of ischemic brain areas (16). Despite case reports, randomized studies showing the efficacy of IV r-tPA in ischemic stroke did not report seizures as an adverse event (17,18,19). In our study, we did not report any patient with status epilepticus who was treated with thrombolytic treatment. We found lower mRS scores at discharge in patients who were treated with IV r-tPA, possibly due to recanalization. Milder stroke in patients who were treated with IV r-tPA could explain the fewer post-stroke seizures.

Endovascular treatment is recommended as the first step treatment when IV r-tPA is contraindicated in patients with acute ischemic stroke and large vessel occlusion. The combination of IV r-tPA and endovascular treatment is recommended within 6 hours of symptom onset in patients with proximal carotid occlusion. According to these data, IV r-tPA should be initiated within 4.5 hours and endovascular treatment should be initiated within 6 hours after the beginning of symptoms (20). For endovascular treatment, patients should fulfill the following criteria: mRS score 0 or 1 prior to stroke, treated with IV r-tPA within 4.5 hours of acute ischemic stroke, proximal occlusion of internal or middle carotid artery, age >18 years, NIHSS score >6, ASPECT score >6, beginning treatment within 6 hours of symptom onset (21).

In our clinic, endovascular treatment was performed to patients with large vessel occlusion in whom IV r-tPA was contraindicated and to patients with large vessel occlusion who did not respond to IV r-tPA due to heavy clot load. This is the first study to address the relationship between etiologies, recanalization degrees, and post-stroke seizures in patients who underwent endovascular treatment. Of 28 patients who were treated with endovascular treatment, 9 had seizures. There was a statistically significant relation between endovascular treatment and epileptic seizures. All patients who underwent endovascular treatment had mRS >5 and had large vessel occlusion, which caused more seizures in these patients.

No statistically significant difference was found between recanalization degrees (total, partial or no recanalization) and seizure frequency. Finding the etiology of stroke prior to endovascular treatment is important. Management can differ according to whether a lesion is caused by atherosclerotic occlusion or cardioembolism (direct thrombectomy or balloon dilatation). There was no statistically significant difference between the different etiologies (large vessel occlusion or cardioembolism) and seizure frequency in patients who received endovascular treatment.

We had 13 patients with malignant middle cerebral artery infarction who underwent decompressive craniectomy and survived for 1 year. Seizure frequency was 38.5% in this group of patients, and we found a statistically significant relation between decompressive craniectomy and seizure frequency. Patients with decompressive craniectomy and seizures have a potential risk for a lower quality of life. Even one seizure may lead a decline in their already medically at-risk status. These patients have large infarctions with cortical involvement and are candidates for epilepsy. Moreover, decompressive craniectomy causes traumatic brain injury, which increases the risk of epilepsy development.

Some studies showed that severity of stroke could predict post-stroke seizures (22). Zhang et al. (23) found a statistically significant relation between severity of stroke and seizures in their meta-analysis. We found a strong relation between post-stroke seizures and mRS at discharge ($p>0.001$). We found larger vessel atherosclerosis as an etiology of stroke in patients who had post-stroke seizures, which was compatible with Killpatrick et al.'s (24) findings. Some studies from Turkey showed that post-stroke seizures were more common in patients with cardioembolism, whereas others showed that seizures were more common in patients with atherothromboses (25,26). Cortical infarction can develop due to atherothrombosis as due to cardioembolism and can lead to post-stroke seizures (27). The first studies showing the relation between cardioembolism and post-stroke seizures were observational studies performed in a limited number of patients before the widespread use of ECHO and imaging techniques. In a large prospective study, no relation was found between cardioembolism and post-stroke seizures (28). Similarly, the National Institute of Neurological Disorders and Stroke trial found no relation between cardioembolism and post-stroke seizures. Data showing the relation between cardioembolism and post-stroke seizures are not adequate (29). AED use in post-stroke seizures is still being discussed. AEDs can be used if seizures recur frequently. In neurosurgical diseases such as subarachnoid hemorrhage and brain tumors, prophylactic AED use is avoided due to the low seizure incidence in patients with stroke and adverse events caused by some old AEDs (30). The rate of prophylactic AED use was 10% in our study, which is compatible with the study by Santamarina et al. (31), and we could not find any relation between primary prophylaxis and seizures, which could be probably caused by initiation of prophylactic AEDs by physicians to patients who were at higher risk of developing seizures. A Cochrane analysis suggested double-blind and placebo-controlled studies to show whether prophylactic AEDs would prevent seizures (32). Clinical studies are required to investigate the efficacy of prophylactic AEDs that are initiated to prevent post-stroke seizures. Such a study was designed but could not be performed. The reasons for rejecting participation in the study were fear of adverse events and the probability of not receiving medication (placebo), which constituted the experimental nature of the study, and also relatives of the patients did not want to impose extra burden to their family members through participation in the study (33).

Conclusion

According to our findings, patients with mRS 4 and 5 at discharge, patients who did not respond to IV r-tPA treatment and were treated with endovascular treatment due to heavy clot load, and patients who underwent decompressive craniectomy had the

highest risk for developing seizures. Clinical studies are required to investigate the efficacy of prophylactic AEDs that are initiated to prevent post-stroke seizures. Performing double-blind, placebo-controlled studies to analyze the efficacy of prophylactic AEDs in the group of patients with the highest risk of developing seizures is not possible and because of this, prospective observational drug studies are needed.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Eskisehir Osmangazi University, Faculty of Medicine on September 29th, 2014 (8058721/353).

Informed Consent: Patient approval is not necessary because it is a retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Y.D., G.T.U., Concept: Y.D., G.T.U., Design: Y.D., G.T.U., Data Collection or Processing: Y.D., G.T.U., Analysis or Interpretation: Y.D., G.T.U., B.E., Literature Search: Y.D., G.T.U., Writing: Y.D.

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