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Identifying the Risk Factors of Early Neurological Deterioration After Thrombolysis in Patients with Acute Ischemic Stroke

Akut İskemik İnmeli Hastalarda Tromboliz Sonrası Erken Nörolojik Kötüleşmenin Risk Faktörlerinin Belirlenmesi

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Abstract

Objective: The efficacy of intravenous (IV) recombinant tissue plasminogen activator (rt-PA) therapy in the treatment of acute ischemic stroke (AIS) has been demonstrated in many studies and IV rt-PA therapy has been increasingly used all over the world. Early neurological deterioration (END) in AIS is common and potentially associated with a poor clinical outcome. The prevalence of END in AIS ranges from 13% to 37% in studies. The aim of this study is to determine the prevalence and risk factors of END in patients with AIS receiving IV rt-PA therapy.

Materials and Methods: One hundred fifty seven patients who were given IV rt-PA treatment by Bursa Uludag University Faculty of Medicine, Department of Neurology between 01.01.2020 and 01.01.2021 were retrospectively included in this study. It was planned to determine the risk group by comparing patients with END with those without.

Results: Age (p=0.023), serum glucose level (p=0.045), The National Institutes of Health Stroke score at discharge (p<0.01), Alberta Stroke Program Early CT (ASPECT) score (p<0.01) when clinical, radiological and demographic data associated with END were evaluated and, statistically significant correlation was found with the presence of major vessel occlusion (p=0.012), ischemic stroke due to cardioembolism (p=0.002), clinical outcome (p<0.001) and symptomatic intracerebral hemorrhage (p<0.001). When the significant variables associated with END were evaluated with binary logistic regression, the most significant variables were found to be age (p=0.006) and ASPECT score (p<0.001).

Conclusion: The causes of END are multifactorial. The most associated risk factors were found to be advanced age and low ASPECT score. It was understood that the most common cause of END was the inability to perform mechanical thrombectomy for major vessel occlusion. Contrary to popular belief, the most common cause of END in patients with AIS who received IV rt-PA treatment was not considered to be symptomatic intracranial hemorrhage but to inadequate recanalization or late recanalization.

Keywords: Intravenous rt-PA therapy, early neurological deterioration, ASPECT score

Öz

Amaç: Akut iskemik inme (Aİİ) tedavisinde intravenöz (İV) rekombinant doku plazminojen aktivatörü (rt-PA) tedavisinin etkinliği birçok çalışmada gösterilmiş ve İV rt-PA tedavisi tüm dünyada giderek artan bir şekilde kullanılmaya başlanmıştır. Aİİ'de erken nörolojik kötüleşme (ENK) yaygın bir durumdur ve potansiyel olarak kötü klinik sonlanım ile ilişkilidir. Aİİ'de ENK prevalansı yapılan çalışmalarda %13 ile %37 arasında değişmektedir. Bu çalışmanın amacı İV rt-PA tedavisi alan Aİİ'li hastalarda ENK prevalansının ve risk faktörlerinin belirlenmesidir.

Gereç ve Yöntem: Bu çalışmaya 01.01.2020-01.01.2021 tarihleri arasında Bursa Uludağ Üniversitesi Tıp Fakültesi, Nöroloji Anabilim Dalı tarafından İV rt-PA tedavisi verilmiş 157 hasta retrospektif olarak dahil edildi. ENK olan hastalar, olmayanlar ile kıyaslanarak riskli grubun belirlenmesi planlandı.

Bulgular: ENK ile ilişkili klinik, radyolojik ve demografik veriler değerlendirildiğinde yaş (p=0,023), serum glukoz düzeyi (p=0,045), taburculuktaki *The National Institutes of Health Stroke* skoru (p<0,01), *Alberta Stroke Program Early CT* (ASPECT) skoru (p<0,01), majör damar oklüzyonu varlığı (p=0,012), kardiyoembolizme bağlı iskemik inme (p=0,002), klinik sonlanım (p<0,001) ve semptomatik intraserebral kanama (p<0,001) ile anlamlı istatistiksel ilişki saptandı. ENK ile ilişkili anlamlı değişkenler binary lojistik regresyon ile değerlendirildiğinde en anlamlı değişkenlerin yaş (p=0,006) ve ASPECT skoru (p<0,001) olduğu saptandı.

Sonuç: ENK sebepleri multifaktöriyeldir. Risk faktörlerinden en ilişkili olanları ileri yaş ve düşük ASPECT skoru olarak saptanmıştır. ENK'nın en sık sebebinin ise majör damar oklüzyonuna mekanik trombektomi yapılamaması olduğu anlaşıldı. Sanılanın aksine İV rt-PA tedavisi alan Aİİ'li hastalarda ENK'nın en sık sebebi semptomatik intrakraniyal kanama değil yetersiz rekanalizasyon ya da geç rekanalizasyon olarak değerlendirildi.

Anahtar Kelimeler: İntravenöz rt-PA tedavisi, erken nörolojik kötüleşme, ASPECT skoru

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Introduction

Acute ischemic stroke (AIS) is one of the leading causes of disability and death in the world, affecting one in six adults with approximately 3-6 million stroke cases per year (1). The efficacy of intravenous recombinant tissue plasminogen activator thrombolysis (IVT) in the treatment of AIS has been demonstrated in many studies, and IVT has been increasingly applied all over the world (2,3).

Early neurological deterioration (END) is common and associated with poor functional outcome. The prevalence of END in AIS ranges from 13% to 37% (4,5,6,7). This wide range may be due to differences in the definition of END. There are several possible mechanisms such as inadequate collateralization, clot progression, recurrent stroke, brain edema, hemorrhagic transformation, re-occlusion of the recanalized artery and seizures, that may cause END in AIS (8).

AIS is a heterogeneous disease in which many complex mechanisms are involved. In addition, risk factors of ischemic stroke show ethnic and racial differences. The aim of this study is to determine the prevalence and predictors of END in patients with AIS treated with IVT.

Materials and Methods

This study retrospectively included 157 patients who were treated with IVT in Bursa Uludag University, Faculty of Medicine, Department of Neurology between 01.01.2020-01.01.2021.

The Clinical Research Ethics Committee of the Bursa Uludag University, Faculty of Medicine approved the study (13 April 2022; 2022-8/7). Since it was a retrospective study, a consent form was not required. Eligible patients were treated with IVT according to international clinical guidelines (9).

Inclusion criteria were as follows: Age ≥18 years and admission within the first 4.5 hours of symptom onset. An upper or a lower "The National Institutes of Health Stroke Scale" (NIHSS) score threshold was not chosen. Exclusion criteria were; intracranial hemorrhage in computed tomography (CT), systemic hemorrhage, the presence of frank hypodensity indicating established brain infarction, and "Alberta Stroke Program Early CT" (ASPECT) score of 4 or less. All patients were monitored hourly by using NIHSS for the first 24 hours after IVT start and twice a day after the first 24 hours. An NIHSS score increase of 2 or more in the first 72 hours was considered END (10). NIHSS scoring was performed by neurologists as part of the clinical routine.

Patients with a non-disabling stroke and with NIHSS score <4 who were admitted within the first 4.5 hours of their symptom onset were observed during the treatment window for progression of symptoms. In our center, CT is the initial preferred imaging modality in patients admitted to the emergency department with focal neurological deficits. If intracranial hemorrhage is not seen in the CT, CT angiography is routinely performed. Signs of early ischemia on CT were evaluated and ASPECT scores were calculated for all included patients. Presence of large vessel occlusion (LVO) was evaluated on CT angiography. The examined large vessels were internal carotid artery, M1 and M2 segments of middle cerebral artery and basilar artery. As recommended in international stroke guidelines; mechanical thrombectomy (MT) was performed in patients with ischemic stroke with LVO with a pre-stroke "modified Rankin Scale" (mRS) score lower than 2, and with an NIHSS score of 6 or more (9). Follow up CT was done either 24 hours after treatment or in case of END, and all imaging studies were evaluated by a neuroradiologist.

Symptomatic intracerebral hemorrhage (SICH) was defined as local or distant type 2 parenchymal hemorrhage occurring <36 hours following treatment and causing NIHSS decrease of ≥4 points according to the criteria of "The Safe Implementation of Thrombolysis in Stroke-Monitoring Study" (11).

In patients without SICH in control brain CT, stroke etiologies were evaluated using the TOAST stroke classification, and treatments for stroke etiology were initiated. The clinical outcome of the patients was evaluated in the neurology outpatient clinic on the 90th day. Those with mRS of 0.1, 2 were evaluated as good clinical outcome, and those with 3-6 as poor clinical outcome. We sought to identify predictors of END by comparing patients with and without END.

Statistical Analysis

Patients with AIS who received IVT were categorized as those who developed END and who did not. The radiological, demographic and clinical data of both groups were compared. Statistical analysis was performed using the IBM SPSS Statistics 25.0 package (IBM Corp., Armonk, New York, USA). Shapiro-Wilk test and Q-Q plot were used to determine normality of the distribution of the data. Means and standard deviations or medians (25%-75% quartiles) were then used for analysis of continuous variables. Frequencies and percentages were given for categorical variables. Independent sample t-test or Mann-Whitney U test was used to analyze differences in terms of continuous variables between groups. Fisher Exact test and Pearson chi-square test were used to analyze the differences in terms of categorical variables between groups. Binary logistic regression analysis was used to identify independent risk factors for END in patients with AIS who received IVT. $P<0.05$ was considered statistically significant. Receiver operating characteristic (ROC) analysis was performed to determine the cut-off values of the ASPECT score and age.

Results

One hundred fifty-seven patients, 65 (41.4%) females and 92 (58.6%) males, were included in this study. One hundred eighteen (75.2%) patients had hypertension, 61 (38.9%) diabetes mellitus, 84 (53.5%) coronary artery disease, 78 (49.7%) atrial fibrillation (AF) and 69 (43.9%) patients were smokers. Twenty-seven (17.2%) patients had ischemic stroke due to large artery atherosclerosis, 84 (53.1%) cardioembolism (CE), 8 (5.1%) small-vessel occlusion, 4 (2.4%) stroke of other determined etiology and 35 (22.2%) stroke of undetermined etiology.

One hundred fifty-seven patients were treated with IVT. The mean onset-to-needle time (OTN) of the patients was

190.41±50.23 minutes. LVO was observed in 77 (49%) patients. MT was performed in 47 (29.9%) patients. MT was not performed in 10 patients with NIHSS score <6, and 20 (12.7%) patients who had a pre-stroke mRS score of >2. The mean NIHSS score of patients with AIS was 16.00±7.45 on admission and 10.51±10.31 at discharge. END was observed in 32 (20%) patients. Fifty-five (35%) patients had poor clinical outcome and 102 (64.9%) had good clinical outcome.

END was associated with age (p=0.023), serum glucose level (p=0.045), NIHSS score at discharge (p<0.01), ASPECT score (p<0.01), the presence of LVO (p=0.012), ischemic stroke due to CE (p=0.002), clinical outcome (p<0.01) and symptomatic intracranial hemorrhage (p<0.001). However, END was not associated with gender, hypertension, diabetes mellitus, coronary artery disease, AF, smoking, systolic blood pressure, diastolic blood pressure, creatinine value, NIHSS score before IVT treatment, severity of leukoaraiosis, stroke due to LVO, OTN and MT (p>0.05) (Table 1).

In binary logistic regression, the most significant variables were found to be age [p=0.006, Odds ratio (OR):1.077] and the ASPECT score (p<0.001, OR: 1.278) (Table 2).

The ROC analysis was performed to determine the cut-off values of age and the ASPECT score. The cut-off value for ASPECT score and END was 7 [p<0.001, area under the curve (AUC): 0.721, sensitivity: 68.7%, specificity: 72.8%]. The cut-off value for age and END was 78 (p<0.020, AUC: 0.630), sensitivity: 43.7%, specificity: 81.6% (Table 3, Figure 1).

The causes of END were as follows: Not undergoing MT due to pre-stroke mRS score >2 in 12 patients, SICH in 9 patients, futile recanalization in 4 patients, concomitant aortic dissection in 1 patient, and END of unknown cause in 6 patients (Table 4).

Discussion

The incidence of END was found to be 20% in patients with AIS treated with IVT, and the incidence of poor functional outcome was increased in patients with END. To date, few

Table 1. Comparison of acute ischemic stroke patients with and without early neurological deterioration

	Patients with early neurological deterioration (n=32)	Patients without early neurological deterioration (n=125)	p value
Age* mean ± SD	74.96±10.42	68.12±2.72	**0.023**
Gender** (male gender)	21 (65.62%)	71 (56.80%)	0.336
Hypertension**	23 (71.87%)	95 (76.00%)	0.630
Diabetes mellitus**	17 (53.12%)	44 (35.20%)	0.253
Coronary artery disease**	20 (62.50%)	64 (51.20%)	0.253
Atrial fibrillation**	16 (50.00%)	62 (52.00%)	0.968
Smoking**	12 (37.50%)	57 (45.60%)	0.410
Glucose (mg/dl)* mean ± SD	165.23±76.12	137.23±52.47	0.045
Systolic blood pressure* mean ± SD	153.45±24.23	152.45±24.24	0.984
Diastolic blood pressure* mean ± SD	87.62±11.28	88.28±15.66	0.876
Creatinine (mg/dl)*	1.043±0.41	1.02±0.71	0.521
NIHSS score before IVT* mean ± SD	17.12±7.41	15.71±7.46	0.292
NIHSS score after IVT* mean ± SD	24.71±6.76	6.87±7.53	**<0.001**
ASPECT score*	7.68±1.87	9.12±1.14	**<0.001**
Severity of leukoaraiosis* mean ± SD	2.37±3.02	1.82±3.01	0.239
The presence of LVO**	22 (68.75%)	55 (44.10%)	**0.012**
Ischemic stroke due to atherosclerotic vascular disease**	4 (12.5%)	23 (18.40%)	0.430
Ischemic stroke due to cardioembolism**	25 (78.12%)	59 (47.20%)	**0.002**
Symptom-needle time (minutes)* mean ± SD	189.37±55.60	190.68±49.01	0.983
Mechanical thrombectomy*	10 (31.25%)	37 (29.60%)	0.85
Hemorrhagic transformation**	9 (28.12%)	10 (8%)	**0.001**
Symptomatic intracerebral hemorrhage**	9 (28.12%)	0 (%)	**<0.001**
Clinical outcome** *(poor clinical outcome)*	29 (90.62%)	33 (26.40%)	**<0.001**

Significant variables are shown in bold. *Mann-Witney U test, **Pearson chi-square test/continuty correction test/Fisher Exact test, SD: Standard deviation, IVT: Intravenous thrombolysis, ASPECT: Alberta Stroke Program Early CT score, LVO: Large vessel occlusion, NIHSS: National Institutes of Health Stroke Scale

studies have analyzed the relationship between END and prognosis (12).

In previous studies, factors associated with END were found to be advanced age, systolic blood pressure at admission, diabetes mellitus, and severity of stroke (4,7,13,14,15,16,17). The causes of END are multifactorial. In our study, factors associated with END in patients with AIS treated with IVT were advanced age, presence of LVO, serum glucose level, ASPECT score, ischemic stroke due to cardioembolism, and symptomatic intracranial hemorrhage. The predictors of END were found to be age and ASPECT score.

Advanced age is the most notable and irreversible risk factor for AIS and is an important predictor of clinical outcome (18). The incidence of ischemic stroke increases rapidly with age in both genders, doubling every decade after the age of 55 (19). More than a third of all acute strokes occur in people aged 80 years, and the incidence of stroke will continue to increase in this age group due to increased life expectancy (20). As we found in line with the literature, the probability of developing AF in elderly patients was found to be significantly higher than in younger patients (21,22). AF is associated with a five-fold increased risk of ischemic stroke, but anticoagulation can reduce the risk of recurrent stroke by 60%. Although more than one-third of patients over the age of 80 have AF, only 13.6% are treated with oral anticoagulants (23,24). In addition, AF is an independent risk factor for LVO (25). Many studies have shown the association of advanced age with symptomatic intracranial hemorrhage and poor clinical outcome. Possible causes of END in elderly patients may include more LVO due to AF, the failure of patients with LVO to benefit from IVT, and not performing MT in patients with mRS score greater than 2.

In our study, one of the factors associated with END in patients with AIS who received IVT was the presence of LVO.

Table 2. Evaluation of significant variables for early neurological deterioration with binary logistic regression

	p value	Odss ratio	%95 CI lower-upper
Age	**0.006**	1.077	1.022-1.136
Glucose (mg/dl)	0.157	1.006	0.998-1.014
ASPECT score	**<0.001**	1.278	0.363-0.742
The presence of LVO	0.634	1.27	0.465-3.55
Cardioembolic stroke	0.248	1.90	0.638-5.682
Hemorrhagic transformation	0.069	3.27	0.913-11.780

Significant variables are shown in bold. Significance of the model: p<0.001. CI: Confidence interval, ASPECT score: Alberta Stroke Program Early CT score, LVO: Large vessel occlusion

Possibly thanks to good collateralization, some patients with AIS with LVO may present with mild deficits. Although IVT is standard in these patients, the risk of END and poor functional outcome has been emphasized (26,27,28).

In patients with minor deficits and LVOs, it has been shown that the cause of END is not intracranial hemorrhage, but rather the enlargement of the ischemic area due to inadequate recanalization (29).

The variable with highest association with END was found to be the ASPECT score in this study. The ASPECT score was developed to detect early ischemic changes in patients with AIS. The use of the ASPECT score becomes widespread as recanalization treatments are increasingly used. In the international stroke guidelines, recanalization treatments are recommended for patients with AIS with an ASPECT score of 6 or higher. ASPECT score has been associated with END in most studies.

SICH, the most devastating cause of END, occurred in 9 (5.7%) patients. Although the incidence of symptomatic intracranial hemorrhage was found to be 6.2% in the NINDS study and 6.2% in the ECASS 2 study, the incidence of symptomatic intracranial hemorrhage was found to be less than 6% in recent studies (2,3,30).

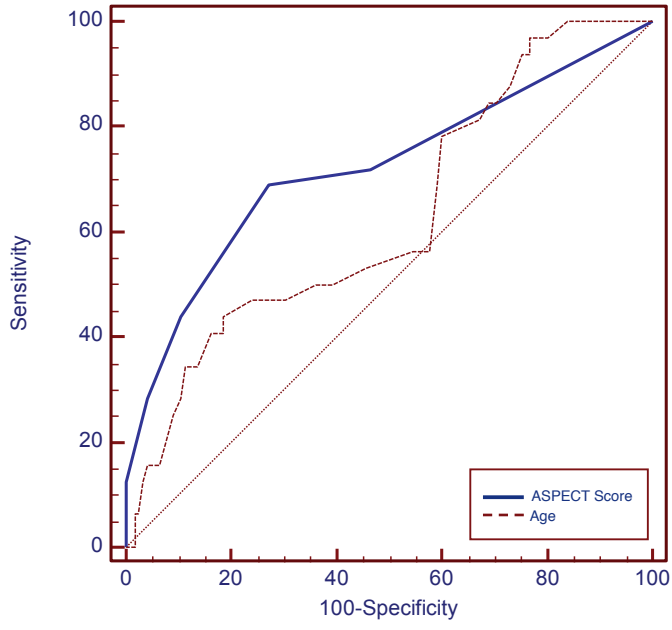

Figure 1. Comparison of area under the curve for independent risk factors for early neurological deterioration

Table 3. Diagnostic characteristics of risk factors for early neurological deterioration after thrombolysis

	p value	AUC	Cut-off value	Sensitivity	Specificity	Comparison of AUC values
ASPECT score	<0.001	0.721	7	68.7%	72.8%	p=0.338
Age	0.020	0.630	78	43.7%	81.6%	

ASPECT score: Alberta Stroke Program Early CT score, AUC: Area under the curve

Table 4. Causes of early neurological deterioration	
1. Not performing mechanical thrombectomy in patients with large vessel occlusion and prestroke mRS score ≥2	12
2. Symptomatic intracranial hemorrhage	9
3. Futile recanalization	4
4. Aortic dissection	1
5. Undetermined	6
Total	32

mRS: Modified Rankin Scale

Conclusion

LVO was present in most of the patients (49.1%) who received IVT in our study. The most common cause of END was considered to be failure to perform MT in patients with LVO. Contrary to popular belief, the most common cause of END in patients with AIS who received IVT was not SICH but it was inadequate recanalization or late recanalization. END is multifactorial and its causes are varied. Advanced age and low ASPECT score are independently associated with END. The major limitation of our study was its retrospective nature and small sample size. Due to multifactorial nature of END, our findings based on a small sample cannot be generalized and national multicenter prospective studies are advised.

Ethics

Ethics Committee Approval: Approval for the study was obtained from Bursa Uludag University Faculty of Medicine Clinical Research Ethics Committee with the letter dated 13 April 2022 and numbered 2022-8/7.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Y.D., R.Ö., B.H., M.B., Concept: Y.D., R.Ö., Design: Y.D., R.Ö., Data Collection or Processing: Y.D., R.Ö., Analysis or Interpretation: Y.D., R.Ö., B.H., M.B., Literature Search: Y.D., R.Ö., Writing: Y.D., R.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

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