Factors Associated with Early Recovery after Intravenous Thrombolytic Therapy in Acute Ischemic Stroke

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ABSTRACT

Introduction: In this study, we aimed to identify the factors associated with early neurological improvement (ENI) in acute stroke patients treated with intravenous recombinant tissue plasminogen activator (IV rt-PA), and to determine the association between ENI and outcomes at 3 months after stroke.

Methods: Patients with acute ischemic stroke who were treated with IV rt-PA within 4.5 hours of symptom onset from February 2009 to December 2016 were included in the study at the stroke center of Eskişehir Osmangazi University Medical Faculty. ENI was defined as an improvement in National Institutes of Health Stroke Scale (NIHSS) score of ≥ 8 points compared to the pretreatment score or an NIHSS score of 0 or 1 at 24 hours after stroke. We assessed the outcomes at 3 months after treatment using the modified Rankin Scale (mRS) score, and mRS scores of 0–1 were defined as ‘very good’ outcomes.

Results: ENI was observed in 43.9% of 355 patients included in the study. Very good outcome at the 3rd month was detected in 80.1% of the patients with ENI, and in 15.6% of the patients without ENI ($p < 0.001$).

Patients with ENI were younger ($p = 0.025$), and had lower NIHSS scores ($p = 0.027$) and higher ASPECT scores ($p = 0.008$) than those without. The ENI group had lower serum glucose levels at the time of admission ($p < 0.001$). Additionally, the presence of diabetes mellitus, hypertension, and hyperdense artery sign were more frequent in the ENI group ($p = 0.001$, $p = 0.024$, and $p < 0.001$, respectively). Finally, multiple regression analysis showed a significant relationship between serum glucose level, hyperdense artery sign, and ENI.

Conclusion: There is a significant relationship between ENI and very good outcome at 3 months in acute stroke patients who received IV rt-PA. Therefore, the management of factors such as serum glucose level, NIHSS score, ASPECT score and presence of hyperdense artery sign which are related to ENI, and the determination of treatment strategies according to them are important issues for achieving a better outcome in acute ischemic stroke.

Keywords: Acute stroke, rt-PA, thrombolysis, outcome, recovery

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INTRODUCTION

Stroke is one of the most important causes of disability, and death in developed countries, and 80% of all strokes worldwide are ischemic strokes (1, 2). Cerebral angiographies performed shortly after stroke onset demonstrated that 80% of these strokes were due to arterial occlusion (3, 4). Previously, standard medical treatments for acute ischemic stroke were used; however, the treatment of ischemic stroke has dramatically changed in 1995. It was demonstrated that the intravenous recombinant tissue plasminogen activator (IV rt-PA) improves the outcome if applied within the first three hours of stroke onset (5). In addition,

in 2008, the results of *The European Cooperative Acute Stroke Study III* (ECASS III) study showed that this treatment was effective between the first 3–4.5 hours (6). According to the results of *The National Institute of Neurological Disorders and Stroke* (NINDS) study group, at least 30% of patients treated with IV rt-PA continue their lives with a mild deficit or no deficit after three months (5). Furthermore, it is thought that

early neurological improvement (ENI) after 24 hours of treatment can independently predict the clinical outcome at the end of the third month, and may be a sign of a good outcome (7, 8).

Detection of the factors associated with ENI after IV rt-PA may be important issues in predicting the outcome, as well as in selection of the patients and regulation of the associated factors for a better outcome. Therefore, we aimed to identify the factors associated with ENI in acute stroke patients treated with IV rt-PA, and to determine the association between ENI and outcomes at three months after stroke in our stroke center.

METHODS

This retrospective study included acute ischemic stroke patients treated with IV rt-PA within 4.5 hours of symptom onset, between February 2009 and December 2016 at Eskişehir Osmangazi University Stroke Center.

Patients with acute posterior circulation stroke, and who underwent endovascular intervention after IV rt-PA were excluded from the study. IV rt-PA was given according to 'The European Stroke Organization' guidelines; 10% of the total dose (0.9 mg/kg, maximum dose=90 mg) was administered as a bolus dose and the rest was infused over one hour (9). Demographic features, vital, and laboratory findings at the time of admission, medical history, previous medications, pre-treatment and 24-h National Institutes of Health Stroke Scale (NIHSS) scores, pre-treatment *Alberta Stroke Program Early CT* (ASPECT) scores on computed tomography (CT) of patients, and the time between symptom onset and the treatment were recorded.

ENI was defined as a NIHSS score of 0–1 or a reduction in the score by ≥ 8 points at 24 h when compared to the pretreatment score, and this 8-point difference had a sufficient sensitivity to differentiate the treatment and placebo groups without overlapping in confidence intervals according to NINDS study (5, 7). Outcomes of the patients were determined by the modified Rankin Scale (mRS) scores at the 3rd month, and mRS scores of 0–1; were defined as 'very good outcome' or 'complete recovery'. We used *The Safe Implementation of Thrombolysis in Stroke* (SITS) definition for symptomatic intracerebral hemorrhages (sICH); type 2 parenchymal hemorrhages causing a neurological deterioration of ≥ 4 NIHSS points from baseline or leading to death (10).

This study was carried out considering Helsinki Declaration criteria, and approval of the ethics committee was taken from the ethics committee of Eskişehir Osmangazi University Medical Faculty.

Statistical Analysis

We analyzed the relationship between pre-treatment clinical, demographic, and radiological data of the patients received IV rt-PA with acute ischemic stroke and ENI at 24 hours after treatment. Data were checked for normality using the Shapiro-Wilk W-test.

The Mann-Whitney U test was used to compare unevenly binary distributed groups.

Pearson Exact Chi-Square, Continuity Correction Chi-Square, and Fisher's Exact Chi-Square tests were used to analyze the cross tables. Logistic regression analysis was performed to determine the factors associated with ENI. A two-sided p value less than 0.05 was considered statistically significant.

RESULTS

A total of 355 patients (199 male) were included in the study. The mean age of the patients was 65, and the mean time between symptom onset and treatment was 154 min. The mean NIHSS score at the time of admission was 14.5 and the ASPECT score was >7 in 88% of the patients. 36.1% of the patients had a hyperdense artery sign on pre-treatment CT.

ENI was observed in 43.9% of patients at the 24 h after IV rt-PA. According to the outcomes at the 3rd month, very good outcome (mRS 0–1) was found in 125 (80.1%) of 156 patients with ENI, and in 31 (15.6%) of 199 patients without ENI ($p<0.001$) (Figure 1). None of the patients with ENI developed sICH, and the rate of sICH was statistically lower in these patients ($p<0.005$) (Table 1).

Patients were dichotomized into two groups: those with ENI versus those without, and the variables that may be associated with ENI were assessed. Patients with ENI were younger ($p=0.025$) and they had lower NIHSS scores ($p=0.027$), and higher ASPECT scores ($p=0.008$), compared to those without. In addition, the ENI group were less likely to have a history of diabetes mellitus (DM) or hypertension (HT) ($p=0.001$ and $p=0.024$,

Figure 1. Comparison of mRS scores of the groups with and without ENI at the 3rd month

respectively), and the serum glucose levels of this group were lower than the other group ($p<0.001$). The presence of a hyperdense artery sign was also lower in the ENI group ($p<0.001$). No significant association was found between other variables and ENI. The findings are summarized in Table 1.

Finally, according to logistic regression analysis, when the baseline serum glucose level increased by one unit (1 mg/dl); the rate of ENI was reduced by 1.008 times, and the presence of a hyperdense artery sign decreased the rate of ENI by 2.393 times (Table 2).

Table 1. Comparison of data of patients with and without ENI

Variable	ENI (positive) n=156	ENI (negative) n=199	P Value
Very good outcome (mRS 0–1), n (%)	125 (80.1)	31 (15.6)	<0.001
Symptomatic hemorrhage, n (%)	0 (0)	12 (6)	0.005
Male, n (%)	92 (59)	107 (53.8)	0.327
Age, mean (SD)	64 (10.9)	66 (11.3)	0.025
Baseline NIHSS score, median (IQR)	14 (4.5)	16 (5)	0.027
Baseline ASPECT score, median (IQR)	9 (1)	9 (1.2)	0.008
Dominant hemisphere, n (%)	76 (48.7)	105 (52.8)	0.449
Time to thrombolysis, min, mean (SD)	151 (50.2)	157 (52.8)	0.511
Hyperdense artery sign, n, (%)	39 (25)	89 (44.7)	<0.001
Vascular risk factors, n (%)			
Hypertension	91 (58.3)	139 (69.8)	0.024
Diabetes mellitus	34 (21.8)	75 (37.7)	0.001
Hyperlipidemia	73 (46.8)	95 (47.7)	0.860
Atrial fibrillation	56 (35.9)	67 (33.7)	0.661
Stroke	18 (11.5)	27 (13.6)	0.682
Baseline glucose (mg/dL), mean (SD)	133.3 (49.5)	159.4 (70)	<0.001
Baseline SBP (mmHg), mean (SD)	141.9 (24.2)	143.8 (21.5)	0.487
Baseline DBP (mmHg), mean (SD)	83.5 (13)	84.2 (11.6)	0.428

ENI=early neurological improvement; mRS=modified Rankin Scale; NIHSS=National Institutes of Health Stroke Scale; ASPECT=Alberta Stroke Program Early CT; SBP=systolic blood pressure; DBP=diastolic blood pressure

Table 2. Results of logistic regression analysis

Variable	95% CI	B (Coefficients)	SE	OR	P Value
Hyperdense artery sign	1.501–3.815	0.873	0.238	2.393	<0.001
Baseline glucose (mg/dL)	1.004–1.012	-0.008	0.002	1.008	<0.001
Constant		0.310	0.358		0.387

CI=confidence interval; B=unstandardized coefficients; SE=standard error; OR=odds ratio;

DISCUSSION

According to the results of our study, ENI was observed in 43.9% of acute stroke patients who received IV rt-PA and 'very good outcome' was found significantly higher in patients with ENI (positive predictive value=0.80, negative predictive value=0.84). Similarly, Saposnik et al. also found early recovery after 24 hours in their study as an independent predictor of good outcome at the 3rd month (11).

There were differences in the definition of this dramatic improvement between studies, and we used the definition of NINDS study which is descriptive enough to distinguish the placebo and treatment group (5). In NINDS study, when the 8-point difference in the NIHSS score was reduced to 4, it was not enough to distinguish the two groups. However, when it was increased to 10, the number of cases was insufficient. This early recovery is considered to be an indicator of arterial recanalization, and early reperfusion of brain tissue, and previously, the relationship between successful recanalization and early recovery has been demonstrated by transcranial Doppler studies (12, 13).

In the two studies with similar designs, Yaghi et al. found early recovery more frequent in younger patients, and in patients without atrial fibrillation, whereas Saposnik et al. found it more frequent in female gender, and in patients with a glucose level <8 mmol/L, and without cortical involvement on brain imaging at 24 h (11, 14). In our study, age, baseline NIHSS score, and ASPECT score, presence of a hyperdense artery sign, serum glucose level at admission, and a history of HT or DM were found to be significantly associated with ENI. In the multiple regression analysis, there was a significant correlation between baseline serum glucose level, and presence of a hyperdense artery sign and ENI. According to them, the patients with ENI were younger than those without. In the NINDS study, an inverse relationship was found between age and good outcome at the 3 month, but this effect was observed both in the IV rt-PA group, and in the placebo group (5). In the randomized analysis of 9 studies involving 6756 patients, age did not change the effect of IV rt-PA on good outcome (15). Therefore, it is likely that the effect of age on the good outcome in our study is a biological effect (7).

Ten different regions in the brain are evaluated for ASPECT scoring and if there is no evidence of ischemia in a region; 1 point is given for this region, otherwise; 0 point is given (16).

Accordingly, the total score decreases as the presence of early ischemic changes increases. In our study, patients with ENI were found to have higher ASPECT scores and this relationship has been revealed previously (17, 18). Absolute cerebral blood flow, and duration of ischemia are the determinants of infarct formation, and ASPECT score may be indicative of the severity of stroke and the time between symptom onset and CT imaging (18). However, we did not find any relationship between the time between symptom onset and treatment and the ASPECT score. This may be related to the fact that the vast majority of our patients had an ASPECT score >7. The differences between the patients who had ASPECT score above this value seemed to provide the development of ENI. Additionally, the NIHSS scores of the patients with ENI were significantly lower than

those without. This indicates a relationship between the severity of stroke and ENI. The NIHSS score, and the changes in this score after treatment may provide information about the arterial occlusion area. When the proximal arterial occlusions are compared with the distal ones, they are accompanied by a higher baseline NIHSS score which may also predict a 3-month outcome (19). Thus, the NIHSS score may help us to choose appropriate patients for IV rt-PA or endovascular intervention.

Hyperglycemia is independently associated with a larger final infarct volume, and poor clinical outcome which may occur despite recanalization (20, 21). Hyperglycemia disturbs collateral circulation of ischemic penumbra, increases the reperfusion injury, and has harmful effects on the outcome in stroke with major vessel occlusion via increasing blood brain barrier permeability, decreasing fibrinolytic activity, anaerobic glycolysis, and free radical production (22). However, hyperglycemia is not associated with poor outcome in lacunar strokes which usually do not contain a penumbra (23). We found that the rate of ENI decreased when the baseline serum glucose level increased. Furthermore, the group without ENI was more likely to have DM and HT and it is known that both HT and DM are independently associated with poor outcome (24, 25, 26).

In addition, another important result of our study was a 2.5-fold decrease in the rate of ENI with the presence of hyperdense artery sign. Hyperdense artery sign is a well-defined sign of thromboembolic arterial occlusion, and is associated with more severe stroke and worse outcome (27, 28). Although Manelfe et al. showed that IV rt-PA provides a better neurological recovery in patients with proximal or distal hyperdense middle cerebral artery signs compared to placebo in the analysis of *The European Cooperative Acute Stroke Study I* (ECASS I), IV rt-PA had low efficacy in patients with large arterial occlusion such as internal carotid artery or proximal of middle cerebral artery (27, 29, 30). In our study, hyperdense artery signs have not been classified regarding to their locations. Nevertheless, the results suggest that the patients with hyperdense artery sign are less likely to have a good outcome, and these patients may be candidates for endovascular intervention.

Our study has some limitations. Prospective collection and retrospective analysis of data, and the non-randomized design of the study may have led to bias. Apart from this, we did not classify hyperdense artery signs regarding to their locations, and did not evaluate post-treatment recanalization angiographically or ultrasonographically; this may have prevented us from achieving more accurate results.

In conclusion, ENI at 24 hours after IV rt-PA is significantly correlated with a very good outcome or complete recovery at the 3rd month. Furthermore, baseline serum glucose level, NIHSS and ASPECT score, and presence of hyperdense artery sign were also found to be associated with ENI in addition to unchangeable factors such as age, history of DM, and HT. Therefore, management of these factors and determination of treatment strategies according to them are important issues for achieving a better outcome in acute ischemic stroke.

Ethics Committee Approval: It was taken from Eskişehir Osmangazi University Faculty of Medicine Ethics Committee.

Informed Consent: Because the study was retrospective and the patient identities were not specified, written patient consent was not taken from the patients participating in this study.

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REFERENCES

1. Truelsen T, Ekman M, Boysen G. Cost of stroke in Europe. *Eur J Neurol* 2005;12:78–84. [CrossRef]
2. J Bogousslavsky, Liu M, Moncayo J, Norrving B, Tsiskaridze A, Yamaguchi T, Yatsu F. Neurological disorders; a public health approach, Chap 3.9. Stroke. In: Neurological disorders, Public Health Challenges. Switzerland: WHO Press; 2006. p.151–163.
3. Fieschi C, Argentino C, Lenzi GL, Sacchetti ML, Toni D, Bozzao L. Clinical and instrumental evaluation of patients with ischemic stroke within the first six hours. *J Neuro Sci* 1989;91:311–321.
4. del Zoppo GJ, Poeck K, Pessin MS, Wolpert SM, Furlan AJ, Ferbert A, Alberts MJ, Zivin JA, Wechsler L, Busse O, Greenlee R Jr, Brass L, Mohr JP, Feldmann E, Hacke W, Kase CS, Biller J, Gress D, Otis SM. Recombinant tissue plasminogen activator in acute thrombotic and embolic stroke. *Ann Neurol* 1992;32:78–86. [CrossRef]
5. National Institute of Neurological Disorders and Stroke tPA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;333:1581–1587. [CrossRef]
6. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, Larrue V, Lees KR, Medeghri Z, Machnig T, Schneider D, von Kummer R, Wahlgren N, Toni D; ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008;359:1317–1329. [CrossRef]
7. Brown DL, Johnston KC, Wagner DP, Haley EC Jr. Predicting major neurological improvement with intravenous recombinant tissue plasminogen activator treatment of stroke. *Stroke* 2004;35:147–150. [CrossRef]
8. Johnston KC, Connors AF Jr, Wagner DP, Knaus WA, Wang X, Haley EC Jr. A predictive risk model for outcomes of ischemic stroke. *Stroke* 2000;31:448–455.
9. European Stroke Organisation (ESO) Executive Committee; ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis* 2008;25:457–507. [CrossRef]
10. Mazya M, Egidio JA, Ford GA, Lees KR, Mikulik R, Toni D, Wahlgren N, Ahmed N; SITS Investigators. Predicting the risk of symptomatic intracerebral hemorrhage in ischemic stroke treated with intravenous alteplase: safe Implementation of Treatments in Stroke (SITS) symptomatic intracerebral hemorrhage risk score. *Stroke* 2012;43:1524–1531. [CrossRef]
11. Saposnik G, Di Legge S, Webster F, Hachinski V. Predictors of major neurologic improvement after thrombolysis in acute stroke. *Neurology* 2005;65:1169–1174. [CrossRef]
12. Demchuk AM, Burgin WS, Christou I, Felberg RA, Barber PA, Hill MD, Alexandrov AV. Thrombolysis in brain ischemia (TIBI) transcranial Doppler flow grades predict clinical severity, early recovery, and mortality in patients treated with intravenous tissue plasminogen activator. *Stroke* 2001;32:89–93.
13. Alexandrov AV, Burgin WS, Demchuk AM, El-Mitwalli A, Grotta JC. Speed of intracranial clot lysis with intravenous tissue plasminogen activator therapy: sonographic classification and short-term improvement. *Circulation* 2001;103:2897–2902.
14. Yaghi S, Hinduja A, Bianchi N. Predictors of major improvement after intravenous thrombolysis in acute ischemic stroke. *Int J Neurosci* 2016;126:67–69. [CrossRef]
15. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, Brott T, Cohen G, Davis S, Donnan G, Grotta J, Howard G, Kaste M, Koga M, von Kummer R, Lansberg M, Lindley RI, Murray G, Olivot JM, Parsons M, Tilley B, Toni D, Toyoda K, Wahlgren N, Wardlaw J, Whiteley W, del Zoppo GJ, Baigent C, Sandercock P, Hacke W; Stroke Thrombolysis Trialists' Collaborative Group. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet* 2014;384:1929–1935. [CrossRef]
16. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. *Lancet* 2000;355:1670–1674.
17. Demchuk AM, Hill MD, Barber PA, Silver B, Patel SC, Levine SR; NINDS rtPA Stroke Study Group, NIH. Importance of Early Ischemic Computed Tomography Changes Using ASPECTS in NINDS rtPA Stroke Study. *Stroke* 2005;36:2110–2115. [CrossRef]
18. Hill MD, Demchuk AM, Tomsick TA, Palesch YY, Broderick JP. Using the baseline CT scan to select acute stroke patients for IV-IA therapy. *AJNR Am J Neuroradiol* 2006;27:1612–1616.
19. Osaki M, Miyashita F, Koga M, Fukuda M, Shigehatake Y, Nagatsuka K, Minematsu K, Toyoda K. Simple clinical predictors of stroke outcome based on National Institutes of Health Stroke scale score during 1-h recombinant tissue-type plasminogen activator infusion. *Eur J Neurol* 2014;21:411–418. [CrossRef]
20. Poppe AY, Majumdar SR, Jeerakathil T, Ghali W, Buchan AM, Hill MD; Canadian Alteplase for Stroke Effectiveness Study Investigators. Admission hyperglycemia predicts a worse outcome in stroke patients treated with intravenous thrombolysis. *Diabetes Care* 2009;32:617–622. [CrossRef]
21. Vaidya VR, Rao AK, Mozzoli M, Homko C, Cheung P, Boden G. Effects of hyperglycemia and hyperinsulinemia on circulating tissue factor procoagulant activity and platelet CD40 ligand. *Diabetes* 2006;55:202–208.
22. Miedema I, Luijckx GJ, Brouns R, De Keyser J, Uyttenboogaart M. Admission hyperglycemia and outcome after intravenous thrombolysis: is there a difference among the stroke-subtypes? *BMC Neurol* 2016;16:104. [CrossRef]
23. Uyttenboogaart M, Koch MW, Stewart RE, Vroomen PC, Luijckx GJ, De Keyser J. Moderate hyperglycaemia is associated with favourable outcome in acute lacunar stroke. *Brain* 2007;130:1626–1630. [CrossRef]
24. Hu G, Sarti C, Jousilahti P, Peltonen M, Qiao Q, Antikainen R, Tuomilehto J. The impact of history of hypertension and type 2 diabetes at baseline on the incidence of stroke and stroke mortality. *Stroke* 2005;36:2538–2543. [CrossRef]
25. Jia Q, Zhao X, Wang C, Wang Y, Yan Y, Li H, Zhong L, Liu L, Zheng H, Zhou Y, Wang Y. Diabetes and poor outcomes within 6 months after acute ischemic stroke: the China National Stroke Registry. *Stroke* 2011;42:2758–2762. [CrossRef]
26. Tanaka R, Ueno Y, Miyamoto N, Yamashiro K, Tanaka Y, Shimura H, Hattori N, Urabe T. Impact of diabetes and prediabetes on the short-term prognosis in patients with acute ischemic stroke. *J Neurol Sci* 2013;332:45–50. [CrossRef]
27. Manelfe C, Larrue V, von Kummer R, Bozzao L, Ringelb P, Bastianello S, Iweins F, Lesaffre E. Association of hyperdense middle cerebral artery sign with clinical outcome in patients with tissue plasminogen activator. *Stroke* 1999;30:769–772. [CrossRef]
28. Novotna J, Kadlecova P, Czlonkowska A, Brozman M, Švigelj V, Csiba L, Körv J, Demarin V, Vilionskis A, Mikulik R; SITS-EAST Investigators. Hyperdense cerebral artery computed tomography sign is associated with stroke severity rather than stroke subtype. *J Stroke Cerebrovasc Dis* 2014;23:2533–2539. [CrossRef]
29. Saqqur M, Uchino K, Demchuk AM, Molina CA, Garami Z, Calleja S, Akhtar N, Orouk FO, Salam A, Shuaib A, Alexandrov AV; CLOTBUST Investigators. Site of arterial occlusion identified by transcranial Doppler predict the response to intravenous thrombolysis for stroke. *Stroke* 2007;38:948–954. [CrossRef]
30. Endo S, Kuwayama N, Hirashima Y, Akai T, Nishijima M, Takaku A. Results of urgent thrombolysis in patients with major stroke and atherothrombotic occlusion of the cervical internal carotid artery. *AJNR Am J Neuroradiol* 1998;19:1169–1175.