



PARAMETERS AFFECTING STROKE SEVERITY AND OUTCOME IN ACUTE STROKE PATIENTS TREATED WITH IV THROMBOLYSIS

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Abstract

Aim: Our aim is to evaluate vascular risk factors and laboratory findings in patients treated with IV thrombolysis, to compare these parameters according to neurological findings scored by a National Institutes of Health Stroke Scale (NIHSS) at admission, after 7 days and to investigate the impact of these parameters on stroke severity and outcome at 3rd month.

Methods: We reviewed 53 consecutive acute ischemic stroke patients admitted within 0-4.5 h after stroke onset and treated with IV thrombolysis between 2014 March-2018 May. Patients with acute posterior circulation stroke, and who underwent endovascular intervention after thrombolysis were excluded. Demographic features, vascular risk factors, laboratory findings and hemorrhagic transformation, and NIHSS scores of patients at admission and after 7 days, and also 3rd month mRS scores were recorded.

Results: The mean age of patients was 64.79±12.26 and 60.37 % of them were male. Mean NIHSS score at admission was 10.60±5.16 and one week after IV r-tPA treatment, the mean score was 7.07±5.39. Hemorrhagic transformation was 18.9%. The male ratio was significantly higher in mild-moderate stroke group ($p=0.008$), the prevalence of hypertension, diabetes, hemorrhagic transformation and blood urea levels were also significantly higher in severe stroke group than mild-moderate group ($p<0.05$). In addition neutrophil levels were higher in severe group, but not statistically significant. Creatine levels were significantly higher in the poor outcome group (NIHSS difference <6) after one week.

Conclusion: Female gender, hemorrhagic transformation and high neutrophil levels were found to have impact on stroke severity towards poor prognosis independently.

Key words: IV thrombolysis; stroke severity; clinical outcome; risk factors

1-INTRODUCTION:

Thrombolysis for acute ischemic stroke (AIS) is an acute therapy that can reduce stroke associated disability. Randomized controlled studies have shown that intravenous recombinant tissue

plasminogen activator (IV r-tPA) therapy administered within the first 3 hours after AIS led to a 10% to 30% decrease in the mortality and disability of patients at 3 to 6 months post-treatment (1,2,3). More recently, results from the *European Cooperative Acute Stroke Study*

(ECASS) III randomized trial of IV rt-PA at 3 to 4.5 hours from stroke onset proved that it is also effective beyond 3 hours in selected group of patients (3,4), but that the magnitude of benefit diminishes with increasing treatment delay (5).

To determine factors associated with stroke severity and outcome after IV r-tPA treatment can be important in predicting the outcome and selection of eligible patients, also management of the associated factors for a better 3-6 month outcome (3). Predicting the groups for which this therapy will be most effective is important for minimizing mortality and improving functional outcomes (2). Numerous clinical and laboratory variables have been identified as potential predictors of clinical outcome. Age, stroke severity, hemorrhagic transformation, infarct location, comorbid conditions such as vascular risk factors, clinical findings and laboratory tests including renal functions and coagulation tests may influence stroke prognosis and outcome (6, 7). Furthermore, it was suggested that infarct volume, as measured by CT, has also been shown to correlate with clinical outcome after 7 days of treatment and may independently predict the clinical outcome at the end of the third month (3,7).

We aimed to evaluate vascular risk factors and laboratory findings in patients treated with IV r-tPA, to compare these parameters according to neurological findings scored by a National Institutes of Health Stroke Scale (NIHSS) at admission and after 7 days and also third month modified rankin scores (mRS) and to investigate the effect of these parameters on stroke severity and outcome.

2-METHODS:

2-1: Study Groups:

The study enrolled 53 consecutive acute ischemic stroke patients treated with IV r-tPA within 4.5 hours of symptom onset and who were hospitalized at least seven days, between 2014 March-2018 May retrospectively.

Patients with acute posterior circulation stroke,

and who underwent endovascular intervention after IV r-tPA were excluded from the study. IV r-tPA was given according to 'AHA/ASA Guideline' Guidelines for the Early Management of Patients With Acute Ischemic Stroke'; 10% of the total dose (0.9 mg/kg, maximum dose=90 mg) was administered as a bolus dose and the rest was infused in one hour (8).

Demographic features (age, gender), vital and laboratory findings (renal function tests, coagulation tests, liver enzymes, glucose, uric acids, complete blood count), previous or newly diagnosed vascular risk factors (hypertension (HT), diabetes mellitus (DM), atrial fibrillation (AF), previous stroke (PS), coronary artery disease (CAD)), hemorrhagic transformation in a week, and NIHSS scores of patients on admission and after 7 days, the time between symptom onset and the treatment (0-3 h and 3-4.5 h) and also third month mRS scores were recorded.

In supratentorial infarcts, NIHSS cut-off value for poor outcome was accepted 10, as described by Yoshimura et al. in 2018 from the pooled data of *Enhanced Control of Hypertension and Thrombolysis Stroke Study* (ENCHANTED) trial (9). Accordingly, NIHSS ≥ 10 was accepted as poor outcome and <10 good outcome in our study population as well. The neurological improvement in NIHSS ≥ 6 was defined as good response and <6 was considered as poor response after IV rt PA treatment. Third month functional outcomes were indicated as good outcome (mRS ≤ 2) and poor outcome (mRS >2).

All parameters described above were compared between the groups NIHSS <10 and NIHSS ≥ 10 , NIHSS difference <6 and NIHSS difference ≥ 6 , mRS ≤ 2 and mRS >2 accordingly.

This retrospective study was carried out considering Helsinki Declaration criteria, and approved by the local ethics committee of education and research hospital.

2-2: Laboratory tests:

In the first 24 hours after admission, 10-ml blood samples were obtained for complete blood count

(CBC) and total biochemistry via antecubital vein into two tubes by forming mild stasis. Glucose, urea, creatine, uric acids, CBC (hemoglobin, platelet, leucocytes, neutrophil) aPTT, PT, INR, ALT, AST levels were analyzed for each patient.

2-3: Statistical analysis:

SPSS version 23.0 (IBM Corporation; Chicago, Illinois) was utilized for all statistical analyses. Descriptive statistics and mean values were calculated. Mann Whitney U and Student’s t-tests were used to assess parametric variables. Chi-square test was used to assess nonparametric variables. Binary logistic regression analyses were utilized to evaluate impact of variables on the groups according to stroke outcome and severity. P-values <0.05

were considered to indicate statistical significance.

2-4: Results:

The mean age of patients was 64.79±12.26 and 60.37 % of them was male. Mean NIHSS score at admission was 10.60±5.16 and one week after IV r-tPA treatment, the mean score was 7.07±5.39. 18.86% (n=10) of the patients died in three months (mRS=6).

The ratios of vascular risk factors were HT: 56.6%, DM: 30.2%, AF: 39.6%, PS: 13.2%, CAD: 32.1% respectively. Admission in first 3 h was 84.9% and high enough for good response to IV r-tPA therapy. Hemorrhagic transformation was 18.9%, low as expected in this group.

Table 1: Comparison of parameters between groups according to stroke severity

Parameters	Group 1 (NIHSS<10) n: 27	Group 2 (NIHSS≥10) n: 26	P Value
Age	62.66±12.66	67.00±11.66	0.20
Gender (%male)	77.8 %	42.3%	0.008
AF (%)	29.6 %	50 %	0.13
HT	44.4%	69.2%	0.06
DM	18.5%	42.3%	0.05
PS	18.5%	7.7%	0.24
CAD	22.2%	42.3%	0.11
First 3 h	85.2%	84.6%	0.95
Hemorrhagic T.	7.4%	30.8%	0.03
Urea	33.74±12.09	45.61±18.83	0.008
Creatine	0.98±0.29	1.09±0.37	0.22
Glucose	148.18±59.78	183.65±97.62	0.12
aPTT	25.56±9.21	24.58±4.66	0.63
INR	1.05±0.14	1.07±0.10	0.53
PT	12.75±1.74	13.12±1.31	0.39
WBC	8780±2723	9965±2692	0.11
Neutrophil	5588±2364	6883±2805	0.07
WBC/Neutrophil	1.64±0.31	1.53±0.31	0.20
Lymphocytes	2305±723	2199±827	0.62
Hgb.	13.78±1.64	13.49±2.41	0.61
Plt.	238,592±53,528	253,269±128,367	0.58
Uric acids	5.57±1.71	5.81±2.15	0.64
AST	23.14±13.52	23.88±10.80	0.82
ALT	16.11±7,80	17.84±9,62	0.47

NIHSS: national institute health stroke scale. AF: atrial fibrillation HT: hypertension DM: diabetes mellitus. PS: previous stroke. CAD: coronary artery disease. aPTT: activated partial thromboplastin time. INR: international normalized ratio. PT: prothrombin time. WBC: white blood cell.

Table 1 show. Comparison of parameters between groups according to stroke severity, *Vascular and laboratory parameters were compared between two groups of NIHSS >10 (group 1) and NIHSS ≤ 10 (group 2) at the time of admission were stated in Table 1. The male ratio was significantly higher in Group 1 (p=0.008), the prevalence of HT, DM, hemorrhagic transformation and blood urea levels were also significantly higher in Group 2 than Group 1 (p≤ 0.05). In addition neutrophil levels was higher in Group 2, but not significantly different (p=0.07).*

Table 2: Comparison of parameters between groups according to clinical outcome after r-tPA therapy

Parameters	Group 1 (NIHSS diff. ≥6) n:23	Group 2 (NIHSS diff. < 6) n:30	P Value
Age	65.43±12.15	64.30±12.53	0.74
Gender (%male)	56.5%	63.3%	0.61
AF (%)	43.5%	36.7%	0.61
HT (%)	60.9%	53.3%	0.58
DM (%)	39.1%	23.3%	0.21
PS (%)	8.7%	16.7%	0.39
CAD (%)	34.8%	30.0%	0.71
First 3 h (%)	82.6%	86.7%	0.68
Hemorrhagic T.	17.4%	20.0%	0.81
Urea	36.10±13.30	44.08±19.74	0.08
Creatine	0.94±0.19	1.15±0.43	0.04
Glucose	170.26±93.16	162.00±73.34	0.71
aPTT	24.40±4.21	25.60±9.01	0.55
INR	1.04±0.08	1.08±0.14	0.18
PT	12.63±1.28	13.17±1.70	0.21
WBC	9634±2380	9152±3023	0.53
Neutrophil	6324±2097	6146±3035	0.81
WBC/Neutrophil	1.59±0.32	1.59±0.31	0.99
Lymphocytes	2346±834	2181±724	0.44
Hgb.	13.24±1.99	13.94±2.06	0.21
Plt.	261,347±133,303	233,866±55,253	0.31
Uric acids	5.50±1.74	5.83±2.07	0.54
AST	16.56±9.17	17.26±8.46	0.77
ALT	21.86±7.64	24.76±14.71	0.39

NIHSS: national institute health stroke scale. AF: atrial fibrillation HT: hypertension DM: diabetes mellitus. PS: previous stroke. CAD: coronary artery disease. aPTT: activated partial thromboplastin time. INR: international normalized ratio. PT: prothrombin time. WBC: white blood cell.

Table 2 show. Comparison of parameters between groups according to clinical outcome after r-tPA therapy. *Two groups were composed according to the difference between NIHSS scores on admission*

and one week after IV rt-PA therapy as presented in Table 2. Blood creatine levels were significantly higher in Group 2 (NIHSS difference < 6). Mean level of urea was also higher, but not significantly different (p=0.08).

Table 3: Comparison of vascular risk factors between groups according to functional outcome at the 3rd month.

Parameters	Group 1 (mRS ≤ 2) n:23	Group 2 (mRS > 2) n:30	P Value
Age	63.0±14.08	66.16±10.71	0.35
Gender (%male)	73.9%	50.0%	0.07
AF (%)	43.5%	36.7%	0.61
HT (%)	43.5%	66.7%	0.09
DM (%)	21.7%	36.7%	0.24
PS (%)	8.7%	16.7%	0.39
CAD (%)	26.1%	36.7%	0.41
First 3 h (%)	82.6%	86.7%	0.68
Hemorrhagic T.	17.4%	20.0%	0.81
Urea	39.82±20.57	39.36±13.42	0.92
Creatine	1.10±0.45	0.98±0.21	0.22
Glucose	156.04±95.76	172.90±70.07	0.46
Uric acids	5.68±1.79	5.69±2.05	0.98

mRS: modified rankin scores. AF: atrial fibrillation HT: hypertension DM: diabetes mellitus. PS: previous stroke. CAD: coronary artery disease.

Table 3 show. Comparison of vascular risk factors between groups according to functional outcome at the 3rd month. *The patients were also analyzed according to mRS after three months and there was no significantly different parameter between two groups (mRS ≤ 2 (group 1) and mRS > 2(group 2)) as shown in Table 3. The ratio of males in Group 1 and prevalence of HT in Group 2 were higher, but not statistically significant (p>0.05).*

Table 4: Binary logistic regression analysis of significant parameters

	B	S.E	Wald	df	Sig.	Exp(B)	95%CI for Exp	
							Lower	Upper
Gender (male)	-2.13	0.941	5.148	1	0.023	0.118	0.019	0.748
HT	1.265	1.134	1.246	1	0.264	3.544	0.38	32.68
DM	1.70	0.923	3.409	1	0.065	5.498	.900	33.570
Hemorrhagic T.	3.36	1.381	5.923	1	0.015	28.840	1.924	432.318
Urea	0.024	0.029	0.713	1	0.398	1.025	0.968	1.085
Neutrophil	0.000	0.000	5.208	1	0.022	1.000	1.000	1.001

HT: hypertension DM: diabetes mellitus

Table 4 show. Binary logistic regression analysis of significant parameters. *Logistic regression analyses of two groups (NIHSS ≤ 10 and NIHSS > 10) were performed as shown in Table 4. Female gender, hemorrhagic transformation and high neutrophil levels were found to have impact on stroke severity towards poor prognosis independently.*

In addition, according to logistic regression analyses of the other model with two groups (NIHSS difference < 6, NIHSS difference ≥ 6) revealed that urea or creatine levels were not independent risk factors for stroke prognosis after one week.

3-DISCUSSION:

Thrombolysis is at the milestone of modern management of AIS, with good evidence of its efficacy within 4.5 hour of symptom onset. Intracranial hemorrhagic transformation is the major complication associated with thrombolysis in AIS, and key factors increasing risk of hemorrhage include increasing age, high blood pressure, diabetes and stroke severity (1, 8).

In this retrospective study, we did not demonstrate any meaningful differences between mean ages of all defined groups. But there was a significant difference in terms of gender. The results showed that the ratio of males was higher than females in the study population (60.37%) and also significantly higher in mild-moderate stroke group. Furthermore, males had better functional outcome than females according to mRS scores after three months. In addition, we determined that female gender was an independent risk factor for stroke severity in our study ($p=0.023$ - Exp. (B):0.118- (95%CI [0.019-0.748]).

In accordance with the results of our study, in literature it was proven that the prevalence of stroke in females is lower than males, and several studies have shown that females suffered from more severe strokes, had higher short-term mortality than males, but long-term sex differences in mortality persist up to 5 years after stroke (10, 11,12). Ghosh et al. also reported that female patients had significantly higher incidence of poor outcome, but female gender was not a significant predictor of stroke severity and mortality (6). Additionally, in other studies, parameters of worse functional outcome at 1- and 5-year follow-up, greater mental impairment, and lower quality of life were determined in females compared to males (10, 13).

In our study, there was no difference between

ratios of males and females who had favorable outcome at one week following thrombolysis treatment (NIHSS diff.≥ 6; 56.5% in men versus 43.5% in women; $p=0.61$). In a pooled analysis of three major randomized clinical trials of IV r-tPA, Kent et al. showed that the proportion of males and females with good functional outcomes at 90 days following treatment was similar, whereas among the placebo group, significantly fewer women had good outcomes (15).

We demonstrated that HT and DM were more prevalent in severe stroke group (NIHSS ≥10) significantly. Besides HT was more prevalent, but not statistically significant in the patients with poor outcome after three months (mRS >2) ($p=0.09$).

Observational clinical studies reported that stroke severity measured by the NIHSS was associated with elevated blood pressure (BP) during the acute phase, and predicted poor clinical outcomes of ischemic stroke (16). Further high systolic BP is linked with worse clinical outcome in patients with AIS treated with thrombolysis. Higher systolic BP levels are associated with poor rate of recanalization in acute stroke patients treated with thrombolysis (17).

In addition, diabetes on admission is correlated with stroke progression, poor functional outcomes and mortality. It has been also associated with poor outcomes after reperfusion therapy or hemorrhagic transformation following initial ischemic stroke occurrence (18, 19, 20). Hyperglycemia is independently related with larger final infarct volume; disrupts 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, cerebral edema, and decreasing fibrinolytic activity after thrombolysis (2,3,21).

In the present study, hemorrhagic transformation and mean urea levels were also determined significantly higher in severe stroke group ($P < 0.05$). We also found higher urea and creatine levels in the group of poor prognosis (NIHSS difference < 6) one week after thrombolysis. Renal dysfunction may affect outcome and induce renal anemia, oxidative stress, inflammation, endothelial dysfunction, and paradoxical effects on hemostasis in IV r-tPA treated patients (22).

In literature, it was suggested that chronic kidney disease (CKD) is associated with increased risk of ischemic and hemorrhagic stroke, its severity and the risk of poor outcome and mortality in general population and its presence is an independent risk factor for a worse prognosis after a stroke (22,23,24,25). A possible explanation of cerebro-renal interaction may be because of the similar anatomical and functional vasoregulation of microvasculature features (24,26).

Moreover hemorrhagic transformation was significantly higher in severe stroke group, which is an expected result and also in logistic regression analysis it was concluded as an independent risk factor for stroke severity ($p = 0.015$).

On the other hand, mean level of neutrophil was higher in the severe stroke group on admission, but not significantly different ($p = 0.07$), however it was determined as an independent risk factor for stroke severity in acute stage. We also analyzed leucocytes/ neutrophil ratio in our study, but there was no significant difference among the groups.

Clinical evidences have confirmed that early higher leukocyte and neutrophil counts are associated with larger infarct volumes and increased stroke severity in the acute stage of ischemia (27, 28, 29). High neutrophil count in patients with AIS is related to poor prognosis at 3 months, while low lymphocyte count is predictive of poor neurological improvement during the first week after admission. If neutrophil infiltration is inhibited, the infarct

volume may be significantly reduced and neurological outcome is improved (28,29).

There are some limitations of this study, it was retrospective and the number of the cases was small.

In conclusion according to our results; gender, HT, DM, renal dysfunction and neutrophil counts are the predictive factors of stroke severity on admission. Patients with HT are associated with worse prognosis at third months. Additionally, urea and creatine levels may be related with poor outcome after one week for the patients treated with IV r-tPA. Hemorrhagic transformation, female gender and neutrophil counts are the independent factors of stroke severity on admission. Further prospective randomized larger studies are needed to prove these findings.

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