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Original Research

Retrospective Evaluation of the Results of Low-Dose Intravenous Thrombolytic Therapy in Acute Ischemic Stroke

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ABSTRACT

Objectives: This study aimed to investigate the clinical data of patients with acute ischemic stroke who received low-dose intravenous (IV) thrombolytic therapy (0.9 mg/kg; maximum 50 mg) for various reasons, compare the obtained results with those of patients who received standard-dose thrombolytic therapy, and discuss them in light of the literature.

Methods: Patients who received IV thrombolytic therapy within 4.5 h of symptom onset between January 2015 and June 2018 were retrospectively reviewed. Patients were divided into the low-dose group (0.9 mg/kg; max. 50 mg) and the standard-dose group (0.9 mg/kg; max 90 mg) according to the thrombolytic therapy dose, after which demographic data and clinical results were analyzed.

Results: A total of 109 patients receiving thrombolytic therapy (19 patients in the low-dose group and 90 patients in the standard-dose group) were included in the study. There was no significant difference between the two groups in terms of good outcome rates (47.4% vs. 52.2%). There was no statistically significant difference in terms of symptomatic and asymptomatic intracerebral hemorrhage rates.

Conclusion: Our study showed similar efficacy and safety for low-dose IV thrombolytic therapy compared with standard-dose IV thrombolytic therapy administered within 4.5 h of symptom onset in patients with acute ischemic stroke.

Key words: Intracranial hemorrhage, ischemic stroke, thrombolytic therapy

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Studies underpinning intravenous (IV) thrombolytic therapy in acute ischemic stroke (AIS) reported that IV recombinant tissue plasminogen activator (IV r-tPA) (maximum dose: 90 mg) at a standard dose of 0.9 mg/kg had improved functional outcomes in selected patients.[1-4]

On the other hand, standard-dose therapy is linked to the risk of increased symptomatic intracerebral hemorrhage (ICH), leading to mortality, within the first few days after the therapy, independent from the age or the severity of the stroke.[5,6] Therefore, the efficacy and safety of low IV r-tPA dose in the patients with AIS have been investigated.[6-12]

A non-randomized Japanese Alteplase Clinical Trial (J-ACT) that included patients with AIS within 3 h of symptom onset J-ACT[7] demonstrated non-inferior clinical results for the standard-dose effect compared with

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0.6 mg/kg (maximum dose: 60 mg/kg) r-tPA and reported a lower risk for symptomatic ICH. Following J-ACT and other reports in Japan,[8,9] the Japanese Pharmaceuticals Safety Authority endorsed the usage of alteplase at a dose of 0.6 mg/kg as a treatment regimen in AIS.[3] In Asia, low-dose IV thrombolytic therapy is used because it is regarded as efficient and safe, and it is employed as a bridge treatment before scheduled endovascular therapy in the United States.[13] In ENCHANTED, an international, multicenter, randomized, controlled trial, low-dose IV r-tPA (0.6 mg/kg; maximum 60 mg; 15% as an IV bolus and the remaining 85% as a 1-h continuous infusion) made an important step towards being an effective and safer thrombolysis therapy in patients with AIS, which had been administered in the first 4.5 h of symptom onset under tight blood pressure control.[14]

In a meta-analysis, it is also suggested that low-dose r-tPA was effective and safe, and recommended in patients with AIS.[15] In a multicenter, randomized, and prospective study that included mainly Asian patients, significantly less symptomatic ICH was reported with low dose IV r-tPA in AIS. However, the study could not demonstrate the effectiveness of low-dose IV r-tPA treatment.[16]

Currently, the licensed dose for Alteplase in Japan in treating AIS is 0.6 mg/kg, and it is recommended to be administered with a total dose of 0.9 mg/kg (max dose 90 mg) in all treatment guidelines except Japan.[17]

The objective was to examine the clinical data of patients with AIS who had received low-dose IV. r-tPA therapy (0.9 mg/kg; max. 50 mg) for various reasons, compare the obtained results with those of the patients who had received standard-dose thrombolytic therapy and discuss them in accordance with the literature.

Methods

Study Cohort

In this observational, retrospective study, patients who had received IVr-tPA therapy during the first 4.5 h of symptom onset between January 2015 and June 2018 were reviewed. Ischemic stroke was subtyped according to the patients' clinical characteristics.[18] Patients receiving endovascular therapy and patients without follow-up in the next 3 months after stroke were not included. Patients were examined in agreement with the recommendations of the American Heart Association/American Stroke Association 2016 guidelines about indication and contraindication before thrombolytic therapy.[19] 120 patients who had received IV r-tPA treatment were recorded. However, 109 patients who met the required study criteria and whose records were accessed were also included in the study. Patients were evaluated in 2 subgroups according to thrombolytic therapy dose (standard dose and low dose IV r-tPA groups). Patients weighing more than 55 kg were included in the low-dose IV r-tPA group. Accordingly, the standard-dose IV r-tPA group and the low-dose IV r-tPA group consisted of 90 and 19 patients respectively. The weights of the patients receiving low-dose therapy and the reasons for receiving low-dose therapy are presented in Table 1.

The suggested IV r-tPA dose (Actilyse®, Boehringer Ingelheim, Ingelheim, Germany) by the National Institute of Neurological Disorders and Stroke (NINDS) study was administered as a standard dose (10% of the total dose of maximum 90 mg r-tPA calculated from 0.9 mg/kg was administered as IV bolus and the remaining as a 1-h infusion).[1] We administered low-dose thrombolytic therapy, with 10% of the r-tPA total dose calculated from 0.9 mg/kg (maximum 50 mg) given as an IV bolus and the rest as a 1-h infusion.[20] Patients who had complete demographic and clinical characteristics and the ones who had computed tomography (CT) scans of the brain before and 24 h after treatment, and if necessary, afterward, were included in the study. ICH developing within the first 36 h after treatment and responsible for impairment in the general condition was recorded as "symptomatic," and incidentally noticed ICH in follow-up scans as 'asymptomatic.'

Demographic data, symptom/needle time, baseline National Institutes of Health Stroke Scale (NIHSS) scores of the patients, as well as NIHSS scores calculated 24 h after IV thrombolysis were recorded. Early neurologic improvement (ENI) was determined as an NIHSS score of 0 or 1 or an improvement in the score of NIHSS ≥8-point at 24 h post-thrombolytic therapy.[21] The neurologic disability of the patients at 3rd month was determined utilizing the modified Rankin scale (mRS) scores; an mRS score of ≤2 at 3rd month indicated a good functional result. Demographic data and the clinical results were compared between standard dose and low dose IV r-tPA groups.

The study was approved by the Ethics Committee of Kütahya Health Sciences University (date: July 24, 2019, number: 2019/08-4). The current study was carried out in accordance with the Helsinki Declaration.

Statistical Analysis

Using the SPSS 24.0 software (IBM Corp.; Armonk, NY, USA) for statistical analysis, the normality of continuous variables was examined by Kolmogorov-Smirnov test, and the Mann-Whitney U-test was used for comparisons between variables for data not normally distributed. We

expressed the values as median (minimum and maximum) values and, the categorical data were expressed as counts and percentages. We used Chi-square test, Fisher's exact test, and Continuity correction to compare categorical data. $p<0.05$ was accepted as a statistical significance level.

Results

Demographic and Baseline Characteristics of Patients

Of 109 patients with AIS receiving IV thrombolytic therapy comprising the study population, 19 (17.4%) were in the

Table 1. Reasons for patients receiving low-dose thrombolytic therapy

Age (year)	Gender	Reasons for using low-dose treatment	Weight of patients (kg)	Recommended dose based on patients' weight (mg)	Difference of dose (mg)*
62	M	Received one dose LMWH at another hospital (we learned during the IV-tPA treatment and stopped)	60	54	4
53	M	Admission at near the treatment window limit and neurological deterioration during the IV-tPA treatment	74	66.6	16.6
87	F	Renal failure (regular hemodialysis)	80	72	22
66	F	Admission at near the treatment window limit and resistant HT requiring IV antihypertensive therapy	68	61.9	11.9
65	M	Allergic reaction	58	52.2	2.2
57	M	The reason was not stated in patients' medical reports	86	77.4	27.4
62	M	•Renal failure (regular hemodialysis)	78	71.2	21.2
59	M	Received one dose LMWH at another hospital (we learned during the IV-tPA treatment and stopped)	78	71.2	21.2
69	F	Admission at near the treatment window limit and resistant HT requiring IV antihypertensive therapy	100	90	40
73	M	•Received one dose LMWH and presence of several risk factors for bleeding complication	72	64.8	14.8
91	F	•Advanced age and presence of several risk factors for bleeding complication	58	52.2	2.2
68	M	Treatment could not be completed because of delirium	80	72	22
53	M	The reason was not stated in patients' medical reports	75	67.5	17.5
77	F	Resistant HT requiring IV antihypertensive therapy	80	72	22
75	M	Resistant HT requiring IV antihypertensive therapy	82	73.8	23.8
41	M	Admission at near the treatment window limit and resistant HT requiring IV antihypertensive therapy	62	55.8	5.8
74	F	Resistant HT requiring IV Antihypertensive therapy	70	63	13
76	F	Resistant HT requiring IV Antihypertensive therapy	74	66.6	15.6
81	F	•Renal failure	75	67.5	17.5

M: Male; F: Female; LMWH: Low molecular weighted heparin; HT: Hypertension; IV: Intravenous. All of the patients received IV rTPA at a total dose of 50 mg; *: Recommended treatment dose-received treatment dose; •: Patients initially scheduled for low-dose IV rTPA.

Table 2. Comparison of demographic and baseline characteristics of patients in low-dose vs. standard-dose thrombolytic therapy groups

	Low-dose, n=19 (17.4%)	Standard-dose, n=90 (82.6%)	Test statistic	Total, n=109	p
Age (years)	68 (42–91)/47.74	74 (35–92) /56.53	717	73 (35–92)	0.27[a]
>65	12 (63.2)	63 (70)	0.09	75 (68.8)	0.75[b]
Gender, n (%)					
Female	8 (42.1)	46 (51.1)	0.21	54 (49.5)	0.64[b]
Male	11 (57.9)	44 (48.9)		55 (50.5)	
Vascular risk factors, n (%)					
Hypertension	13 (68.4)	59 (65.6)	.00	72 (66.1)	1[b]
Diabetes	2 (10.5)	30 (33.3)	3.93	32 (29.4)	0.08[b]
Hyperlipidemia	7 (36.8)	24 (26.7)	0.37	31 (28.4)	0.54[b]
Atrial Fibrillation	9 (47.4)	41 (45.6)	0.00	50 (45.9)	1[b]
CAD	4 (21.1)	24 (26.7)	-	28 (25.7)	0.77[c]
Smoking	5 (26.3)	33 (36.7)	0.35	38 (34.9)	0.55[b]
SBP (mmHg)	146 (115–220)/53.68	150 (80–200)/55.28	830	150 (80–220)	0.84[a]
DBP (mmHg)	85 (70–120)/65.74	80 (60–120)/52.73	651	83 (60–120)	0.09[a]
Blood glucose level (mg/dL)	127 (97–194)/ 51.26	132 (78–363)/ 55.79	974	130 (78–363)	0.57[a]
Acetyl salicylic acid use, n (%)	5 (26.3)	22 (24.4)	-	27 (25)	0.54[c]
History of stroke	2 (10.5)	4 (4.4)	-	6 (5.5)22	0.28[c]
Clinical stroke type, n (%)					
TACI	8 (42.1)	46 (51.1)	1.52	54 (49.5)	0.67[d]
PACI	9 (47.4)	32 (35.6)		41 (37.6)	
POCI	1 (5.3)	6 (6.7)		7 (6.4)	
Lacunar	1 (5.3)	6 (6.7)		7 (6.4)	
S/N time (min)	150 (79–270)/59.63	150 (60–270)/54.02	767	150 (60–270)	0.48[a]
NIHSS (pre-treatment)	12 (3–20)/42.29	15 (5–26)/57.68	613	14 (3–26)	0.053[a]

CAD: Coronary artery disease; DBP: Diastolic blood pressure; Min.: Minimum; Max.: Maximum; NIHSS: The national institutes of health stroke scale score; S/N: Symptom/needle; SBP: Systolic blood pressure; TACI: Total anterior circulation infarct; PACI: Partial anterior circulation infarct; POCI: Posterior circulation infarct; Data were expressed as median (minimum: maximum)/mean Rank and n (%); a: Mann Whitney U Testi; b: Continuity correction; c: Fisher's Exact Test; d: Pearson Chi-Square.

low-dose IV r-tPA group and 90 (82.6%) were in the standard-dose IV r-tPA group. In the current study, 55 patients were male (50.5%) and the median age of the patients was 73 (range, 35–92) years.

In the standard-dose IV r-tPA group, diabetes was significantly higher as a vascular risk factor (p=0.08). The two groups did not differentiate statistically significantly in terms of symptom/needle time, baseline mean NIHSS scores, glucose concentrations, systolic and diastolic blood pressure values, acetyl-salicylic acid use, and the presence of stroke history. Patients' demographic and baseline characteristics are given in Table 2.

Clinical and Functional Outcomes

A total of 56 patients (51.4%) yielded good functional outcomes (mRS≤2). Nine patients (47.4%) in the low-dose IV r-tPA group and 47 patients (52.2%) in the standard-dose IV r-tPA group had good functional outcomes. The two groups did not differentiate statistically significantly in terms of the 3rd month distribution of good functional outcomes (p>0.05).

A total of 33 patients (30.3%) had ENI. There was not any significant difference in early neurological improvement between the two groups (p=0.68). There was not any significant difference in mean NIHSS scores at 24 h post-treatment (p=0.50). The Asymptomatic ICH rate was high in the standard-dose group, with no statistical significance (13.3–5.3%, p=0.45). Symptomatic ICH was identified in one patient (5.3%) in the low-dose IV r-tPA group versus 3 patients (3.7%) in the standard-dose IV r-tPA group. Mortality was observed in 6 patients (31.6%) in the low-dose IV r-tPA group versus 20 patients (22.2%) in the standard-dose IV r-tPA group, with no significant difference between the two groups (p=0.38). Patients' clinical and functional outcomes are presented in Table 3 and Graphic Fig. 1.

Table 3. Comparison of clinical and functional outcomes in low-dose vs. standard dose thrombolytic therapy groups

Clinical outcomes	Low-dose, n=19, (17.4%)	Standard-dose, n=90, (82.6%)	Test statistic	Total, n=109	*P*
ENI within 24 h, n (%)	7 (36.8)	26 (28.9)	0.16	33 (30.3)	0.68[a]
NIHSS (at 24 h post-treatment)	8 (0–25)/50.61	10 (0–26)/ 55.93	771	9 (0–26)	0.50[b]
aSIH, n (%)	1 (5.3)	12 (13.3)	-	13 (11.9)	0.45[c]
SIH, n (%)	1 (5.3)	3 (3.3)	-	4 (3.7)	0.54[c]
3. month mRS ≤2, n (%)	9 (47.4)	47 (52.2)	0 .00	56 (51.4)	1[a]
Mortality, n (%)	6 (31.6)	20 (22.2)	-	26 (23.9)	0.38[c]

aSIH: Asymptomatic ıntracerebral hemorrhage; ENI: Early neurological improvement; Min.: Minimum; Max.: Maximum; mRS: Modified rankin scale; NIHSS: The national ınstitutes of health stroke scale score; SIH: Symptomatic ıntracerebral hemorrhage; Data were expressed as median (minimum: maximum)/ mean Rank and n (%); a: Continuity correction; b: Mann Whitney U-test; c: Fisher's exact test.

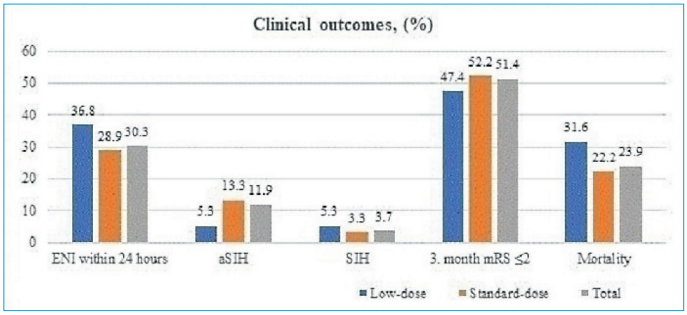

Figure 1. Functional outcomes, intracerebral hemorrhage and, mortality rates in low-dose and standart-dose thrombolytic therapy groups. aSIH: Asymptomatic intracerebral hemorrhage, ENI: Early neurological improvement, mRS: Modified rankin scale, SIH: Symptomatic intracerebral hemorrhage.

Discussion

Many Asian studies on low-dose IV r-tPA in AIS obtained similar clinical outcomes in proportion to the standard-dose IV r-tPA, and low-dose IV r-tPA is commonly used in Asia.[3,7] The efficacy of low-dose alteplase has been investigated in cases where the risk of bleeding was highly likely such as in patients with older age, in cases of scheduled endovascular therapy,[22,23] in patients with impaired renal function,[22,24] or in cases where the time at which stroke began is unclear such as patients with wake-up stroke,[25] in low-income countries where the treatment cost is a concern,[20,26] and in cases of mild stroke.[27] Patients with renal dysfunction who had received IV thrombolytic therapy provided conflicting results regarding mortality, disability, and ICH. Similar results were obtained in the presence of renal dysfunction for low-dose versus standard-dose IV thrombolytic therapy.[24,28] A study that assessed the results of IV thrombolytic treatment in patients aged over 80 years indicated that low-dose IV thrombolytic therapy could be used in patients with low NIHSS. On the other hand, there was no difference in mortality and ICH rates between low-dose versus standard-dose therapy in patients aged over 80 years who experienced a severe stroke; however, the good functional outcomes rate was higher in the patients who received standard-dose therapy. Therefore, it was suggested that treatment options of low-dose and standard-dose IV r-tPA treatment should be offered to patients and their relatives, and information on possible positive and negative differences should be shared.[29]

Although we do not prefer low-dose IV thrombolytic therapy in our practice, we had to administer it in some cases. Mostly, the reasons for applying low-dose thrombolytic therapy were difficulties in reaching the target arterial blood pressure, interrupting the infusion several times due to reincrease in blood pressure, previous use of received low-molecular-weight heparin (LMWH), and presence of renal failure IV thrombolysis is the main treatment for AIS. Thrombolysis-related symptomatic ICH, one of the most scared complications of the treatment,[30] is seen approximately in 6% of the patients and can lead to mortality in approximately 50% of the patients. Although not a contraindication for thrombolytic therapy, prolonged symptom/needle time, high baseline NIHSS score, hypertension, and diabetes history have been shown to be the most significant predictors of the risk for thrombolysis-related symptomatic ICH.[31] atrial fibrillation and cardioembolic strokes have been linked to increased risk and poor prognosis of thrombolysis-related ICH.[32-34] In our study, the presence of diabetes among the vascular risk factors of the two groups was remarkably higher in the standard-dose IV r-tPA group. No significant difference was found among other risk factors.

The symptomatic ICH rate was found 5.8% in the J-ACT[7] trial with low-dose thrombolytic therapy, and 6.4% in the NINDS trial with standard-dose thrombolytic therapy.[1] This rate was reported as 5% in Japan in another low-dose thrombolytic therapy group.[35] Similar rates were seen in our study. The SIH rate was 5.5% in the low-dose IV r-tPA group and 3.3% in the standard-dose IV r-tPA group.

The present guidelines do not suggest the usage of IV thrombolytic therapy for patients who received MWH, rivaroxaban, and other factor Xa inhibitors in the past 24–48 h.[36] However, the study by Xian *et al*.[37] suggested that r-tPA therapy could be considered in chosen patients with AIS receiving factor Xa inhibitors. The patients in whom Rota *et al*.[38] administered thrombolytic therapy while on regular rivaroxaban developed asymptomatic hemorrhagic transformation, which, however, was outweighed by the benefit derived from the thrombolytic therapy, suggesting that the r-tPA therapy can be considered in patients receiving novel oral anticoagulants. Our study showed no significant differences between symptomatic and asymptomatic ICH rates. In the low-dose IV r-tPA group, only one patient had asymptomatic and only one patient had symptomatic ICH. During treatment, we discovered that our patient with asymptomatic ICH had been regularly using a novel oral anticoagulant (rivaroxaban), and our patient with symptomatic hemorrhage had received an effective dose of LMWH before the therapy. For these reasons, we could not complete the standard dose of therapy in our patients.

In this study, the 3rd month good functional outcome rate (mRS ≤2) in the low-dose IV r-tPA group was 47.4% versus 52.2% in the standard-dose IV r-tPA group, with no significant difference. This rate was 35% in a Japanese study with low-dose therapy.[35] The mortality rate was 23.9% (n=26). No patients died due to ICH. The mortality rate in the standard-dose group was 22.2% (n=26) versus 31.6% (n=6) in the low-dose group, with no significant difference. This rate was reported as 9.7% in the J-ACT[7] study, 15% in another Japanese study,[34] and 17% in the NINDS[1] study. Although the study by Liao *et al*.[39] suggested that standard-dose IV r-tPA produced better functional outcomes than low-dose IV r-tPA in patients with AIS without increasing the risk for ICH, meta-analysis studies reported similar efficacy and safety between patients with AIS receiving low-dose IV r-tPA and those receiving standard-dose IV r-tPA.[15]

The study is valuable as it is the first data about the results of low-dose IV thrombolytic therapy in AIS in Turkey. Since our study is retrospective and reflects the small number of results from a single stroke center, our results cannot be generalized to our country.

Conclusion

In summary, a reduction in ICH rates, which is the most feared r-tPA complication, achieved by low-dose therapy may further encourage neurologists to administer this treatment. Similar efficacy with standard-dose therapy and the association with fewer complications and lower costs may be important factors for further widespread use of low-dose thrombolytic therapy. This study showed a similar level of impact and safety for low-dose alteplase therapy compared to the standard-dose thrombolytic therapy administered in the first 4.5 h of symptom onset in patients with AIS. Most of the publications on low-dose IV-rtPA treatment applications were made in Asia. It is known that the rate of intracranial atherosclerosis is higher in the Asian population. According to the present study results, we can speculate that Turkish population may have similarities and similar responses to the Asian population more than Western Societies/population.

Disclosures

Ethics Committee Approval: The study was approved by the Ethics Committee of Kutahya Health Sciences University (No: 2019/08-4, dated: 07.24.2019).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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