Original Article
Intravenous thrombolysis improves one-year outcomes in mild stroke patients

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Abstract: The aim of this study was to evaluate the benefits and risks of intravenous thrombolysis (IVT) in patients with mild strokes after a period of one year. Mild symptoms were defined as an NIHSS score of ≤ 5 points on arrival, in accordance with most prior studies. Between March 2013 and December 2014, 763 consecutive patients diagnosed with acute cerebral ischemia were retrospectively enrolled in this study. Eventually, 240 patients met the eligibility criteria. Of these, 90 patients received IVT and 150 patients did not. Baseline characteristics and outcomes were collected at 3 and 12 months. Multivariable logistic analysis was employed. Patients treated with recombinant tissue plasminogen activator (rt-PA) had higher NIHSS scores on arrival, compared with those that did not receive rt-PA (5 and 2, IQR 4-5 and 1-3, respectively; $P < 0.001$). IVT was independently associated with favorable outcomes at 3 months (OR 7.63, 95% CI 2.82 to 20.64; $P < 0.001$). At 12 months, the effects of IVT on favorable outcomes were maintained (OR 8.04, 95% CI 2.85 to 22.64; $P < 0.001$). Recurrent strokes were more frequent in patients without rt-PA treatment, but IVT did not significantly affect rates of recurrent strokes at either 3 or 12 months. No cases of symptomatic intracranial hemorrhaging were detected. Present results suggest long-term benefits from IVT for mild ischemic strokes, with a low risk of symptomatic intracranial hemorrhaging. In conclusion, IVT is recommended for patients with mild strokes.

Keywords: Acute ischemic stroke, mild stroke, intravenous thrombolysis, stroke outcome

Introduction

Mild or rapidly improving stroke symptoms in patients have increasingly concerned neurologists. A high proportion of these individuals have experienced stroke progression or developed recurrent strokes after conventional therapy with antiplatelet agents and general vascular prevention strategies [1-3]. Several studies have identified that more than half of ischemic stroke patients manifest mild or rapidly improving symptoms at clinical onset [1-3]. Patients with mild strokes that do not receive intravenous thrombolysis (IVT) are at high risk for disability or death [4-6]. Current guidelines recommend the use of IVT for patients with mild strokes within a certain time window [7]. However, mild symptoms are a common reason of withholding IVT even within the standard treatment time window [5] due to concerns about symptomatic intracranial hemorrhaging (sICH). Only 2.7% to 18.0% of time-eligible stroke patients with mild symptoms are treated with recombinant tissue plasminogen activator (rt-PA) [8].

Several recent studies have explored the efficacy and safety of thrombolytic treatment in mild stroke patients, displaying conflicting results [9-14]. The efficacy of rt-PA for mild strokes continues to be debated due to a lack of randomized trial data. Furthermore, most previous studies evaluating the use of IVT in mild stroke patients had limited follow-ups. No studies have included long-term follow-up data. In addition, a consensus definition of mild strokes is still lacking. Several different definitions have been employed in prior studies [8-16]. The most common definition used is the presence of neurological deficits, designated by a National Institute of Health Stroke Scale (NIHSS) score of 5 or less [4, 9-13]. The chief goal of this study was to evaluate the effects of IVT administration for patients with mild strokes (defined as an NIHSS score at presentation of ≤ 5) at the 12-months follow-up time point.

Materials and methods

Ethics statement

This study was conducted in accordance with the Helsinki Declaration. The study protocol was approved by the Ethics Committee of Xin Hua Hospital, Shanghai Jiao Tong University School of Medicine. Written informed consent was obtained from all patients or legal representatives.

Study subjects

This study was a retrospective analysis. Between March 2013 and December 2014, 763 consecutive patients diagnosed with acute cerebral ischemia in the Emergency Department of Xin Hua Hospital were considered for inclusion. Mild symptoms were defined as an NIHSS score of ≤ 5 points on arrival, in accordance with most prior studies [4, 9-13].

Acute ischemic stroke patients meeting the following criteria were included: age 18-80 years, physical signs of brain injury persisting for 1 hour, evidence of acute ischemic stroke on neuroimaging, and baseline NIHSS score ≤ 5. Exclusion criterion included intracranial hemorrhages, pre-morbid modified Rankin Scale (mRS) > 1, absolute contraindications for IVT, endovascular therapy, and missing data on follow-up.

Acute ischemic stroke was diagnosed and managed according to AHA guidelines published in 2007 [17] and the National Guideline for Diagnosis and Treatment of Acute Ischemic Stroke 2010 of China [18]. All patients were admitted into the Stroke Unit. Data, including demographics, risk factors, and laboratory data, were collected. All patients had a CT or MRI brain scan after arrival. Unless contraindicated, follow-up CT angiographies at 24-48 hours were performed. Stroke etiology was classified as large-artery atherosclerosis, cardio-embolism, small vessel occlusion, stroke of other determined etiology, or stroke of undetermined etiology, according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [19]. Eligible patients with no absolute contraindications were treated with intravenous rt-PA at the discretion of treating physicians [17, 18]. A standard dose of 0.9 mg/kg rt-PA (with an upper limit of 90 mg) was administered. Initially, 10% was intravenously injected over 1 minute, followed by continuous infusion of the remaining 90% over 1 hour.

Outcome measurements

NIHSS scores were assessed upon hospital arrival, day 1, and day 7. Functional outcomes by the modified Rankin Scale (mRS) were assessed at 3 and 12 months. A favorable outcome was defined as an mRS score of 0 or 1. An unfavorable outcome was defined as an mRS score of 2-6 points [20, 21]. sICH was defined as any hemorrhaging associated with neurological deterioration (NIHSS score differential ≥ 1 or death) within 7 days (NINDS criteria) [22]. Recurrent stroke occurrence was noted during the follow-up periods. Outcome evaluations were performed via face-to-face interviews by a certified neurologist.

Statistical analysis

Student's t test, Chi-squared test, Fischer's exact test, Mann-Whitney U-test, and One-way ANOVA were employed to assess differences among variables studied. Logistic regression analysis was performed to evaluate the independent effects of thrombolytic treatment on functional outcomes at 3 and 12 months. For multivariable logistic regression, variables associated with outcomes ($P < 0.2$) on univariate analysis were included as covariates. Age, gender, arrival within 4.5 hours after symptoms onset, NIHSS scores on arrival, and intravenous rt-PA treatment were included in the model, regardless of *P*-values. The level of statistical significance was set at $P < 0.05$. Statistical analysis was performed using SPSS software package, version 13.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics of the study cohort

Between March 2013 and December 2014, 763 patients were diagnosed with acute cerebral ischemia in the Emergency Department of Xinhua Hospital. A total of 346 patients had a NIHSS scores ≤ 5 on arrival. However, 38 patients were excluded with age > 80, 51 patients were excluded with pre-morbid mRs > 1, 11 patients were excluded with absolute contraindications for IVT, 4 patients were
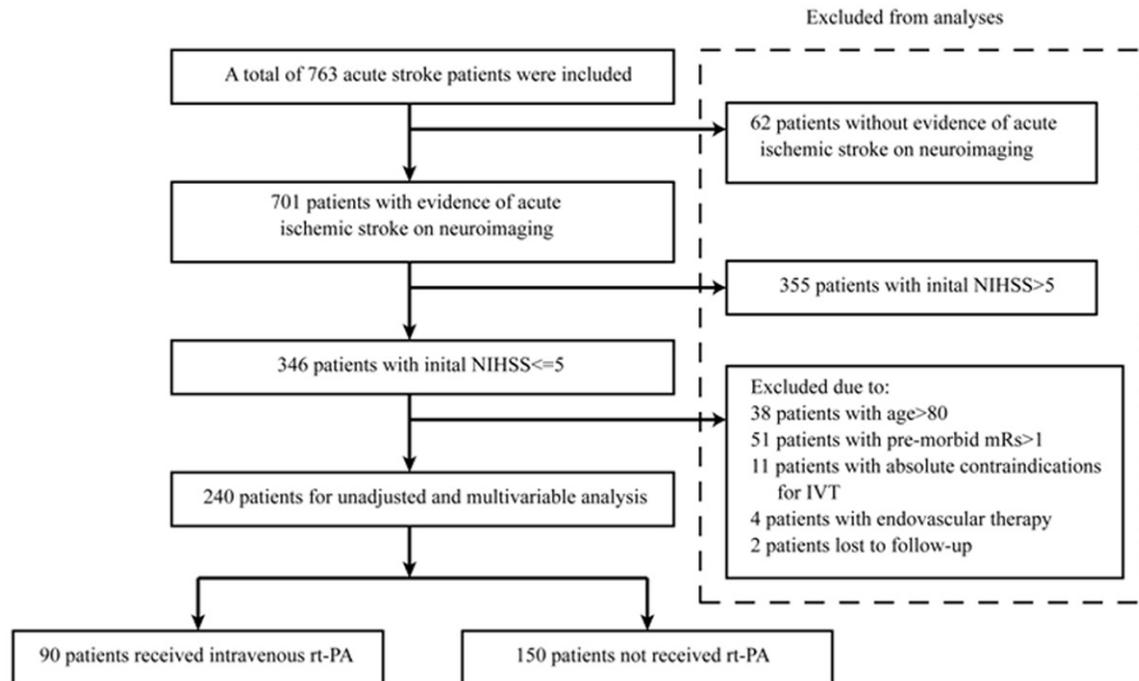
Figure 1. Enrollment of the study subjects.

excluded with endovascular therapy, and 2 patients were excluded due to missing data on follow-up. Ultimately, 240 patients met the eligibility criteria (**Figure 1**). Of these, 90 (37.5%) patients received intravenous rt-PA based on the judgement of the clinical physicians.

The median age among patients with mild strokes receiving rt-PA treatment was less than those that did not receive rt-PA treatment (61 vs. 64, respectively; $P < 0.05$). Patients receiving rt-PA tended to have earlier admission, being admitted within 4.5 hours of symptom onset ($P < 0.001$). Mild stroke patients that did and did not receive rt-PA treatment were comparable in terms of sex, hypertension, coronary heart disease, smoking habits, and previous history of strokes.

Effects of IVT on NIHSS score at 7 days

Patients treated with rt-PA had higher NIHSS scores at admission, compared with those not receiving rt-PA. However, patients treated with rt-PA had a lower median NIHSS score at 7 days than those without rt-PA (**Table 1**). NIHSS scores at 24 hours in the rt-PA group showed a significant decrease from the baseline score. A further decrease was observed in the rt-PA group at 7 days (**Figure 2A**). For patients not

receiving rt-PA, NIHSS scores at 24 hours also showed a large decrease from the baseline score, but NIHSS scores were similar for 24 hours and 7 days (**Figure 2A**). The reduction in NIHSS scores in patients treated with rt-PA was greater than in patients not receiving rt-PA at 24 hours and at 7 days (**Figure 2B**).

Effects of IVT on mRS scores at 3 months and 12 months follow-ups

According to unadjusted analysis, patients receiving rt-PA showed a higher proportion of favorable outcomes than those not receiving rt-PA at both 3 months ($P < 0.05$) and 12 months ($P < 0.05$). The median mRS score among patients with mild strokes receiving rt-PA treatment was lower than those without rt-PA treatment at 3 months ($P < 0.01$).

After adjusting for confounders, intravenous rt-PA was independently associated with favorable outcomes at 3 months (OR 7.64, 95% CI 2.82 to 20.64; $P < 0.001$). At 12 months, the benefit of thrombolytic treatment was maintained (OR 8.04, 95% CI 2.85 to 22.64; $P < 0.001$). Higher NIHSS scores on admission and atrial fibrillation were associated with unfavorable outcomes at 3 months and 12 months (**Table 2**).

Table 1. Characteristics of patients with mild strokes

Characteristics	rt-PA[a] group (n = 90)	No rt-PA group (n = 150)	P
Gender (% male)	62 (68.89%)	101 (67.33%)	0.80
Age, Median [IQR]	61 [55, 69]	64 [58, 74]	0.04
NIHSS[b] score at admission, Median [IQR]	5 [4, 5]	2 [1, 3]	< 0.001
NIHSS score at 24 hours, Median [IQR]	1 [0, 2]	1 [0, 2]	0.74
NIHSS score at 7 days, Median [IQR]	0 [0, 2]	1 [0, 2]	0.001
Arrival within 4.5 h after symptoms onset (%)	100%	24 (16%)	< 0.001
TOAST[c] classification (%)			0.68
Cardio-embolism	19 (21.11%)	24 (16.00%)	
Large artery disease	11 (12.22%)	15 (10.00%)	
Small vessel disease	21 (23.33%)	43 (28.67%)	
Other	0 (0%)	1 (0.67%)	
Undetermined	39 (43.33%)	67 (44.67%)	
Diabetes mellitus	16 (17.78%)	47 (31.33%)	0.02
Hypertension	61 (67.78%)	114 (76.00%)	0.17
Coronary heart disease	13 (14.44%)	15 (10.00%)	0.30
Atrial fibrillation	15 (16.67%)	11 (7.33%)	0.02
Smoking habit	36 (40.00%)	50 (33.33%)	0.30
Previous stroke	6 (6.67%)	8 (5.33%)	0.67
Triglycerides (mmol/L)	2.09 ± 1.37	1.78 ± 1.18	0.07
Glucose (mmol/L)	7.44 ± 3	7.18 ± 2.53	0.49
D-dimer (mg/L), Median [IQR]	0.16 [0.09, 0.35]	0.15 [0.09, 0.27]	0.84
International normalized ratio (INR), Median [IQR]	0.96 [0.92, 1.01]	0.97 [0.92, 1.03]	0.58
3-months mRS[d]	0 [0, 1]	1 [0, 2]	< 0.001
12-months mRS	0 [0, 0]	0 [0, 1]	< 0.001
Functional outcome mRS 0 to 1 (%)			
3-months follow-up	77 (85.6%)	107 (71.3%)	0.01
12-months follow-up	84 (93.3%)	119 (79.3%)	0.004
sICH[e] (%)			
3-months follow-up	0 (0%)	0 (0%)	
12-months follow-up	0 (0%)	0 (0%)	
Recurrent stroke (%)			
3-months follow-up	0 (0%)	5 (3.3%)	0.16
12-months follow-up	0 (0%)	8 (5.4%)	0.03

Values are mean ± SD or median (interquartile range [IQR]) for continuous variables and percentages for categorical variables. [a]Recombinant tissue plasminogen activator; [b]National Institutes of Health Stroke Scale; [c]Trial of Org 10172 in Acute Stroke Treatment [18]; [d]Modified Rankin Scale; [e]Symptomatic intracranial hemorrhage.

Recurrent strokes and symptomatic intracranial hemorrhaging

Recurrent stroke cases were comparable in patients with or without rt-PA treatment at 3 months follow-up (*P* > 0.05), but were more frequent in patients without rt-PA treatment at 12 months. Among patients with mild strokes, 8 cases of recurrent strokes (5.4%) occurred in the 150 patients treated without rt-PA, whereas none occurred in the 90 patients treated with rt-PA (*P* < 0.05). After adjusting for con-

founders, intravenous rt-PA did not significantly affect the rate of recurrent strokes at either 3 or 12 months (**Table 3**). Age and NIHSS scores at admission did not correlate with recurrent strokes (**Table 3**). No cases of symptomatic intracranial hemorrhaging per NINDS criteria were detected among mild stroke patients.

Discussion

According to present results, intravenous rt-PA treatment was independently associated with
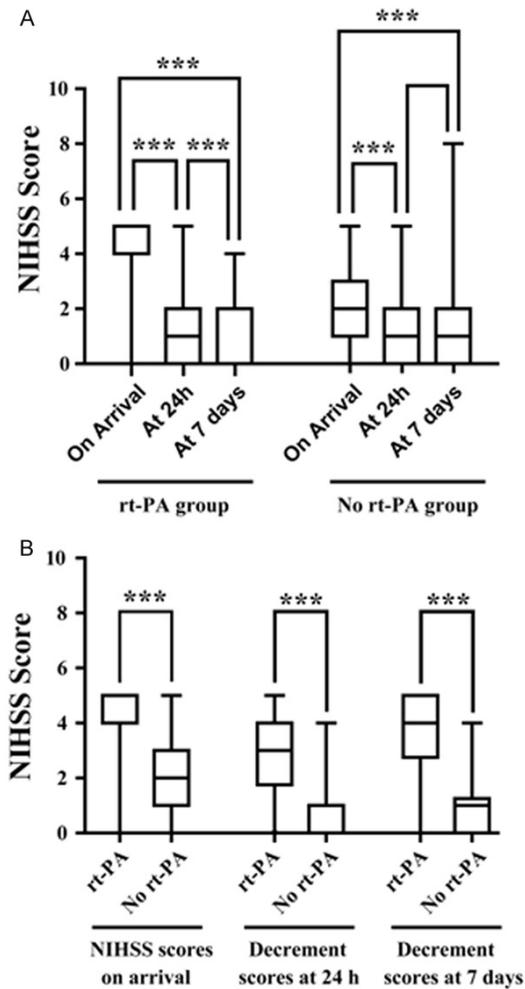
Figure 2. (A) Comparison of NIHSS scores between patients that did and did not receive intravenous rt-PA. For patients receiving rt-PA, the NIHSS score at 24 hours showed a significant decrease from the baseline score (1 and 5, IQR 0-2 and 4-5, respectively; $P < 0.001$), and a further decrease was shown at 7 days (0 and 5, IQR 0-2 and 4-5, respectively; $P < 0.001$). For patients not receiving rt-PA, the NIHSS score at 24 hours also showed a decrease from the baseline score (1 and 2, IQR 0-2 and 1-3, respectively; $P < 0.001$). The NIHSS score were similar between 24 hours and 7 days (1 and 1, IQR 0-2 and 0-2, respectively; $P = 0.20$). (B) The decrement in NIHSS score at different time points for patients that did and did not receive rt-PA. Patients treated with rt-PA had a higher NIHSS score at admission compared with those who did not receive rt-PA (5 and 2, IQR 4-5 and 1-3, respectively; $P < 0.001$). The reduction in NIHSS score in patients treated with rt-PA was greater than that in patients who were not treated with rt-PA at 24 hours (3 and 0, IQR 2-4 and 0-1, respectively; $P < 0.001$; (B)) and at 7 days (4 and 1, IQR 3-5 and 0-1, respectively; $P < 0.001$). Mann-Whitney U-test and one-way ANOVA were used to assess differences. (*** indicates $P < 0.001$.).

long-term favorable outcomes at 12 months in patients with mild strokes. There were low risks of recurrent strokes and symptomatic intracranial hemorrhaging.

There is no universal consensus concerning the definition of mild stroke. Although NIHSS scores do not fully reflect the severity of certain types of strokes (such as posterior circulation strokes), they have been regarded as a convenient tool for quite some time. Most studies on mild stroke patients have employed initial NIHSS scores to define mild strokes. The most common definition is the presence of neurological deficits, designated by an NIHSS score of 5 or less [4, 9-13]. The present study also defined mild symptoms as an NIHSS score of ≤ 5 points on arrival. The benefit from rt-PA treatment among different cut-off points of the NIHSS score was not detected due to a lack of power.

The efficacy of intravenous rt-PA in patients with mild strokes has been debated in the absence of data from randomized controlled clinical trials and long-term follow-up studies. Several observational studies have revealed that rt-PA may be beneficial for patients with mild strokes [9-12]. The Austrian Stroke Unit Registry study suggested that patients with mild deficits benefit from thrombolysis [11]. A Korean registry database showed similar results in relation to the benefits of IVT for mild strokes [9]. Furthermore, a single-center study in Norway suggested that rt-PA treatment was associated with good outcomes in patients with mild strokes [10]. However, other studies have reported no significant benefit from thrombolytic treatment [13, 23]. The third International Stroke Trial (IST-3) included a wider range of patients in evaluating the treatment effects of thrombolytic therapy, but subgroup analysis of mild stroke patients did not show any beneficial effects of rt-PA [14]. Mild strokes have been underrepresented in randomized studies, making further analysis difficult to interpret.

Moreover, outcomes in published research have been defined by 3-months follow-up data. No long-term follow-ups were performed. Present results, which focus on follow-up data 12 months after stroke occurrence, fill in the gap. Present results support the use of intravenous rt-PA for patients with mild strokes, as rt-PA

Table 2. Independent predictors for favorable outcomes in patients with mild strokes

Predictor	mRS[a] 0 or 1 at 3 months		mRS 0 or 1 at 12 months	
	OR (95% CI)	P	OR (95% CI)	P
NIHSS[b] score on arrival	0.62 (0.47, 0.82)	< 0.01	0.67 (0.50, 0.89)	< 0.01
Atrial fibrillation	0.33 (0.12, 0.91)	0.03	0.21 (0.08, 0.60)	< 0.01
Intravenous rt-PA[c]	7.64 (2.82, 20.64)	< 0.001	8.04 (2.85, 22.64)	< 0.001

Adjusted for age, gender, atrial fibrillation, hypertension, diabetes mellitus, NIHSS on admission, intravenous rt-PA treatment, triglycerides, and D-dimer. [a]Modified Rankin Scale; [b]National Institutes of Health Stroke Scale; [c]Recombinant tissue plasminogen activator.

Table 3. Independent predictors for recurrent strokes in patients with mild strokes

Predictor	Recurrent stroke at 3 months		Recurrent stroke at 12 months	
	OR (95% CI)	P	OR (95% CI)	P
NIHSS[a] score on arrival	0.90 (0.44, 1.84)	0.77	0.94 (0.49, 1.78)	0.85
Age	1.09 (0.97, 1.23)	0.13	1.07 (0.98, 1.17)	0.12
Intravenous rt-PA[b]	3.62 (0.00, infinity)	0.98	1.89 (0.00, infinity)	0.99

Adjusted for age, gender, atrial fibrillation, hypertension, diabetes mellitus, NIHSS on arrival and intravenous rt-PA treatment, triglycerides, and D-dimer. [a]National Institutes of Health Stroke Scale; [b]Recombinant tissue plasminogen activator.

patients with more severe strokes and with the greatest potential for rehabilitation.

One reason that mild stroke patients do not receive IVT in regular practice is the assumption of a benign natural course. However, studies have suggested that a sizeable minority of these patients will have a poor recovery [4-6]. Results have shown that patients that do not receive rt-PA treatment have a higher recurrent stroke rate at 12 months, although multivariable analysis has shown that the increase is not statistically significant. Though older patients tend to have recurrent strokes, multivariable analysis has shown that age and NIHSS scores at admission are not associated with recurrent strokes. Due to the small number of recurrent events in the present study, multivariable analysis showed very wide CIs. There may be inadequate power to detect an association between recurrent strokes and rt-PA treatment. Further research with larger sample sizes is necessary to address this issue.

treatment remarkably reduced the 24-hour NIHSS scores for patients with mild strokes, decreasing even further at 7 days. In addition, rt-PA treatment was independently associated with favorable outcomes at 3 months. The beneficial effects of rt-PA were maintained at 12-months follow-up. This phenomenon verified the extended benefits of IVT in mild stroke patients at 12 months, previously unreported. Outcomes for mild stroke patients without rt-PA treatment also showed improvement in terms of NIHSS scores at 24 hours and mRS scores at 12-months follow-up. Differences between patients with and without rt-PA treatment seem to be caused by less improvement, not by a worsening of symptoms.

The risk of sICH in patients with mild strokes receiving rt-PA ranges from 0% to 4.1% in the literature, which is lower than for the overall stroke population [9-12, 24]. In the present study, no cases of sICH were detected in mild stroke patients. This highlights the safety profile of rt-PA treatment in patients with mild strokes.

In the present study, patients receiving rt-PA tended to be younger, had higher NIHSS scores, and had earlier admission, being admitted within 4.5 hours of symptom onset. This suggests that IVT should be administered for

Initial stroke severity has been accepted as the strongest predictor of functional outcomes for ischemic stroke patients [7]. In this study, a higher NIHSS score at arrival was shown to be independently associated with poor outcomes for patients with mild strokes, consistent with previous reports. Atrial fibrillation was verified to be another predictor of poor outcomes for patients with mild strokes.

Late arrival may be the most important reason for withholding thrombolytic treatment [25]. In this study, 126 (84%) patients that did not receive rt-PA missed the time window of 4.5 hours. Inclusion of late-arrival patients in the control group may ensure a more representative group in routine clinical practice. A previous

study showed that early arrival, usually implying active monitoring, was independently associated with excellent outcomes [10]. However, present results did not show a significant effect of arrival time on either 3- or 12-months functional outcomes in patients with mild strokes. This disparity may have resulted from the different proportions of stroke subtypes, race differences, and management of all patients in a dedicated stroke unit.

The main limitation of this study was its non-randomized single-center retrospective study design. Given the differences in demographics at baseline, IVT tends to be administered to patients with more severe strokes and with the greatest potential for rehabilitation. Furthermore, itemized NIHSS scores were not collected. The decision to administer rt-PA may differ based on the nature of the neurologic deficits seen. Therefore, selection bias cannot be excluded. The logistic regression model was adopted to adjust for demographic differences. Because of the small sample size, present conclusions may be due to residual confounding.

In conclusion, present results support the administration of intravenous rt-PA for mild ischemic strokes. Risk of symptomatic intracranial hemorrhaging was quite low. However, future large randomized clinical trials evaluating the benefits of intravenous thrombolysis in patients with mild strokes are warranted.

Disclosure of conflict of interest

None.

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