ORIGINAL ARTICLE

Implementation and Outcome of Thrombolysis with Alteplase 3 to 4.5 h After Acute Stroke in Chinese Patients

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SUMMARY

Background and Purpose: The European Cooperative Acute Stroke Study (ECASS) III showed that intravenous recombinant tissue plasminogen activator (rtPA) administered in the 3 to 4.5 h after symptom onset significantly improved clinical outcomes in patients with acute ischemic stroke (AIS). But little is known regarding the safety and efficacy of intravenous rtPA treatment within this extended time window in Chinese patients with AIS. **Methods and Results:** Data were collected from the Thrombolysis Implementation and Monitor of acute ischemic Stroke in China (TIMS-China). A total of 574 patients who underwent rtPA therapy within 4.5 h after symptom onset were included in this study: 409 in the 0- to 3-h group and 165 in the 3- to 4.5-h group. There were no significant differences in SICH rate (2.4% vs. 1.5%, $P = 0.70$) at 24 to 36 h, mortalities (7.5% vs. 7.3%, $P = 0.84$), independence rate (68.9% vs. 63.9%, $P = 0.19$), and excellent recovery rate (60.9% vs. 52.4%, $P = 0.11$) between the two time window groups. These results were comparable with previous Western studies. **Conclusion:** This study suggests that intravenous rtPA treatment at 3 to 4.5 h of symptom onset remains safe and effective in Chinese patients with AIS.

Introduction

Stroke is the leading cause of disability in China. Intravenous recombination tissue plasminogen activator (rtPA) is the only approved medical therapy for acute ischemic stroke (AIS). Extending the rtPA treatment window is an important strategy for maximizing thrombolytic therapy in patients with AIS. In a pooled analysis, a favorable outcome was observed when thrombolytic treatment was given between 3 and 4.5 h after the onset of symptoms [1]. The European Cooperative Acute Stroke Study (ECASS) III later prospectively confirmed that intravenous alteplase administered between 3 and 4.5 h after the onset of symptoms significantly improved clinical outcomes in patients with AIS, with a higher symptomatic intracranial hemorrhage (SICH) rate, but no change in mortality [2]. Based on this evidence, the guidelines of the European Stroke Organization and the American Stroke Association recommended a new 4.5-h time window for thrombolytic therapy in patients with AIS [3,4]. However, little is known about the safety and efficacy of intravenous rtPA treatment in this extended window in Chinese patients with AIS. The aims of this study were to exam the safety and efficacy of intravenous rtPA treatment given between 3 and 4.5 h after the onset of symptoms

in Chinese patients with AIS and compare the results with Western studies.

Patients and Methods**Study Population and Design**

Data were abstracted from the ongoing project Thrombolysis Implementation and Monitor of acute ischemic Stroke in China (TIMS-China). TIMS-China was a national prospective stroke registry of thrombolytic therapy using intravenous rtPA in patients with AIS. There were 67 major stroke centers nationwide participated in this stroke registry. The study protocol was approved by Ethics Committee of Beijing Tiantan Hospital. The registry was regularly monitored independently by the quality monitoring committee of TIMS-China and the Contract Research Organization. All patients or patients' care providers gave written informed consent before thrombolysis, and all patients were followed up for 3 months.

In this study, we included patients presenting with ischemic stroke who were given intravenous alteplase (Actilyse, Boehringer Ingelheim, Germany) within 4.5 h after symptom onset and

registered in TIMS-China. All patients were fully compliant with product characteristics criteria of Actilyse label. Briefly, patients (1) were between 18 to 80 years of age; (2) received a clinical diagnosis of stroke; (3) had a cerebral tomographic (CT) or magnetic resonance imaging (MRI) scan ruled out hemorrhage, major ischemic infarction, or other nonischemic diseases; (4) had no contraindication for thrombolysis therapy. Thrombolysis treatment was 0.9 mg of alteplase per kilogram (no more than 90 mg), with 10% was administered as a bolus, and the remainder was given by continuous infusion over 60 min. The eligible patients were divided into a 0- to 3-h group and 3 to 4.5-h group according to the time window of thrombolysis.

Main clinical assessments and outcome measures that included in this study were the National Institutes of Health Stroke Scale (NIHSS) at the time of enrollment and 24 h, SICH assessed by CT or MRI and clinical assessment at 24 to 36 h, the modified Rankin scale (mRS) assessed on day 7 and day 90, and death by day 90.

NIHSS is a 15-item scale that measures the level of neurologic impairment. Total scores on the NIHSS range from 0 to 42, with higher values reflecting more severe cerebral infarcts. mRS is a scale that measures the level of disability. Scores on the mRS range from 0 (no symptoms at all) to 6 (death).

Outcome Measurements

The primary outcomes were SICH rate at 24 to 36 h and mortality by 90 days. SICH was evaluated by three different definitions from previous international trials to compare: (1) based on the definition in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) [5], a SICH was defined as an intracerebral hemorrhage type 2 on the 24- to 36-h following-up imaging scan after the start of thrombolysis treatment; combined with a neurological deterioration of four or more points on the NIHSS from the baseline, or from the lowest NIHSS score between the baseline and 24 h after thrombolysis or death. The intracerebral hemorrhage type 2 was defined as a blood clot exceeding 30% of the infarct area, with substantial space occupation; (2) based on the criteria from the National Institute of Neurological Disorders and Stroke (NINDS) study [6], a SICH was defined as a hemorrhage that was not seen on a previous CT scan, and there had subsequently been either a suspicion of hemorrhage or any decline in neurological status; (3) based on ECASS II study [2], a SICH was defined as any intracranial bleeding, with four or more points worsening on NIHSS score.

The secondary outcome was functional recovery assessed by means of the mRS at day 90 (3-month follow-up) by face-to-face clinic visit or telephone interview with the patients or patients' care providers. Functional independence was defined as a mRS score of 0 to 2 [5]. Excellent recovery was defined as a mRS score of 0 to 1 [2].

Statistical Analysis

The chi-square (χ^2) test was used to compare the proportions for categorical variables. The *t*-test or the Mann-Whitney *U*-test was used to compare means or medians for continuous variables. 95% confidence intervals (CI) of proportions were calculated by a score method incorporating continuity correction [6]. Odds ratio (OR)

with its 95% CI and the adjusted OR with its 95% CI were analyzed by univariable and multivariable logistic regression on the efficacy and safety outcomes between the 0- to 3-h group and 3- to 4.5-h group. The adjusted variables included age; sex; history of smoking, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, and previous stroke; independent status prior to the stroke; antiplatelet treatment within 24 h prior to the thrombolytic therapy; antihypertensive treatment; and medical condition at symptoms onset: NIHSS score, blood pressure, blood glucose, and bodyweight. Data of the 3- to 4.5-h group from the TIMS-China stroke registry were compared with those treated in the same time window in the ECASS III study [2], the Safe Implementation of Treatments in Stroke (SITS) study [8], and the Canadian Alteplase for Stroke Effectiveness Study (CASES) [9]. All analyses were performed with SAS software version 9.1.3 (SAS Institute Inc, Cary, NC, USA). A two-sided alpha level of 0.05 was assumed.

Results

Between May 1, 2007 and July 31, 2010, a total of 1221 patients who received intravenous rtPA treatment were registered in the TIMS-china. After excluding the cases with missing data (i.e., time of symptom onset, time of thrombolysis, or the doses of rtPA) ($n = 12$), thrombolysed outside 0- to 4.5-h window ($n = 256$), and violated inclusion criteria of Actilyse label ($n = 379$), 574 patients were included in the current study. Of these, 409 were thrombolysed between 0 and 3 h, and 165 patients were treated between 3 and 4.5 h (Figure 1).

The baseline characteristics of the patients are shown in Table 1. The two groups of patients were comparable. There were more patients had a history of diabetes mellitus in the 0- to 3-h group than those in the 3- to 4.5-h group (14.4% vs. 7.9%, $P = 0.03$). However, there was no significant difference in the mean blood glucose levels at the onset of stroke between the two groups (7.2 vs. 7.4 mmol/L, $P = 0.34$). There was no significant difference in the distribution of stroke subtypes by the Trial of Org 10182 in Acute Stroke Treatment (TOAST) criteria [10].

The primary outcomes, the SICH rate at 24 to 36 h, and the mortalities at day 7 and day 90 are summarized in Table 2. SICH was evaluated by three different definitions from different trials: SITS-MOST, ECASS II, NINDS [2,6,9]. As expected, after adjusting for stroke risk factors and baseline medical conditions, the SICH rates of the 3- to 4.5-h group were slightly higher than those of the 0- to 3-h group, irrelevant to different SICH definitions. There was no difference in mortality at either day 7 or day 90 between the two groups. Interestingly, there was a nonsignificant but strong trend toward better functional recovery in the 3- to 4.5-h group by mRS (Table 2).

The data of thrombolysis at 3- to 4.5-h window from TIMS-China were further compared with those from published international trials: SITS, ECASS III, and CASES. Table 3 showed the comparison of the baseline characteristics of these four trials. In CASES, patients were older and had a wider range of baseline NIHSS score. There was no difference in SICH rates between four trials, by all three of different SICH definitions (Figure 2). The mortality rate at day 90 (3 months) of TIMS-China was similar to that of ECASS III (Figure 3). The mortality rate of CASES was higher than the other three studies. Functional outcomes

Figure 1 Numbers of Eligible Patients.**Table 1** Demographic and baseline characteristics of the patients

Variables	0–3 h (n = 409)	3–4.5 h (n = 165)	P value
Mean age (years)	62.3 ± 10.8	62.2 ± 11.0	0.92
Sex Female (%)	158 (38.6)	58 (35.2)	0.44
Medical history (%)			
Independence (mRS 0–1) prior to stroke	400 (97.8)	162 (98.2)	0.77
Atrial fibrillation	68 (16.6)	39 (23.6)	0.05
TIA	43 (10.5)	14 (8.5)	0.46
Hypertension	224 (54.8)	105 (63.6)	0.05
Diabetes Mellitus	59 (14.4)	13 (7.9)	0.03
Hyperlipidemia	26 (6.4)	7 (4.2)	0.32
Current smoking	148 (36.2)	47 (28.5)	0.08
Previous smoking	172 (42.1)	58 (35.2)	0.13
Previous stroke	52 (12.7)	28 (17.0)	0.18
Mean blood glucose (mmol/L)	7.2 ± 2.2	7.4 ± 2.5	0.34
Receiving antiplatelet drug in 24 h prior to thrombolysis (%)	53 (13.0)	22 (13.3)	0.90
Systolic blood pressure (mmHg)	146.7 ± 19.9	144.4 ± 19.4	0.20
diastolic blood pressure (mmHg)	85.5 ± 11.7	85.2 ± 11.9	0.78
Median NIHSS score (IQR)	11 (7–15)	10 (6–15)	0.48
Median stroke onset to treatment time (IQR) (min)	150 (129–170)	220 (200–245)	<0.0001
Mean weight (kg)	65.0 ± 11.8	68.5 ± 11.8	<0.01
Mean rtPA dose (mg)	58.3 ± 10.6	61.5 ± 10.5	<0.01
Stroke subtype (%)			
Atherothrombotic	219 (53.55)	82 (50.93)	reference
Lacunar	51 (12.47)	11 (6.83)	0.12
Cardioembolic	73 (17.85)	33 (20.50)	0.44
Other/Unknown	66 (16.14)	35 (21.74)	0.16

Variables are mean ± standard deviation or number (%). IQR, interquartile range; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; rtPA, recombinant tissue plasminogen activator; TIA, transient ischemic attack.

Table 2 Safety and function outcomes

Outcome	0- to 3-h group n/N (%; 95% CI)	3- to 4.5-h group n/N (%; 95% CI)	Unadjusted analysis		Adjusted analysis*	
			Odds ratio* (95% CI)	p value	Odds ratio† (95% CI)	p value
SICH (SITS-MOST definition)	6/409 (1.5; 0.3–2.6)	4/165 (2.4; 0.1–4.8)	1.7 (0.5–6.0)	0.66	1.3 (0.3–5.7)	0.70
SICH (ECASS III definition)	10/409 (2.4; 1.0–3.9)	8/165 (4.9; 1.6–8.1)	2.03 (0.8–5.2)	0.13	1.43 (0.4–4.6)	0.54
SICH (NINDS definition)	19/409 (4.7; 2.6–6.7)	9/165 (5.5; 2.0–8.9)	1.18 (0.5–2.7)	0.68	0.93 (0.4–2.5)	0.88
Mortality at 7 days	18/407 (4.4; 2.4–6.4)	7/164 (4.3; 1.2–7.4)	0.96 (0.4–2.4)	0.94	0.99 (0.4–2.8)	0.99
Mortality at 3 months	29/399 (7.3; 4.7–9.8)	12/161 (7.5; 3.4–11.5)	1.03 (0.5–2.1)	0.94	0.92 (0.4–2.1)	0.84
mRS0–2 at 3 months	255/399 (63.9; 59.2–68.6)	111/161 (68.9; 61.8–76.1)	1.25 (0.9–1.9)	0.26	1.36 (0.9–2.2)	0.19
mRS0–1 at 3 months	209/399 (52.4; 47.5–57.3)	98/161 (60.9; 53.3–68.4)	1.41 (1.0–2.1)	0.07	1.44 (0.9–2.2)	0.11

ECASS, European Cooperative Acute Stroke Study; mRS, modified Rankin scale; NINDS, National Institute of Neurological Disorders and Stroke; SICH, symptomatic intracerebral hemorrhage; SITS-MOST, Safe Implementation of Thrombolysis in Stroke-Monitoring Study. *Adjusted for stroke risk factors and baseline medical condition (see Patients and Methods). †Odds ratios were calculated by comparing the 3- to 4.5-h group with 0- to 3-h group.

Table 3 Baseline variables in TIMS-China, SITS, ECASS III, and CASES (3 to 4.5 h).

rtPA treated in 3 to 4.5 h	TIMS-China n = 165	ECASS III n = 418	SITS n = 664	CASES n = 129
Age (years)	62.2 ± 11.0	64.9 ± 12.2	65 (55–73)†	70.3 ± 14.0
Median NIHSS score (IQR)	10 (6–15)	9 (NR)	11 (7–16)	13 (2–31)
Median stroke onset to treatment time (IQR), minutes	220 (200–245)	239 (NR)	195 (187–210)	190 (NR)

Variables are mean ± standard deviation or range. CASES, Canadian Alteplase for Stroke Effectiveness Study; ECASS, European–Australasian Acute Stroke Study; IQR, interquartile range; NR, not reported; SD, standard deviation; SITS, Safe Implementation of Treatments in Stroke study; TIMS-China, Thrombolysis Implementation and Monitor of acute ischemic Stroke in China. †The number showed median age with IQR.

Figure 2 Comparison of SICH (3–4.5 hour) of TIMS-China with those in SITS, ECASS III, and CASES by different definitions.

(independence and excellent recovery) by mRS at day 90 in TIMS-China were again similar to those of ECASS III (Figure 3).

Discussion

Since its approval in the United States in 1996, intravenous rtPA has been the only medical therapy for patients with AIS for over 15 years [2,5,6,8,9,11–13]. Recently, the treatment time window was further extended from 3 h to 4.5 h. There are few published studies regarding the efficacy and safety of rtPA therapy in Asian population. Data from Japan and Taiwan suggested that the lower dose of rtPA resulted in similar treatment effects compared with the standard dose (0.9 mg/kg) [14,15]. It is still questionable

Figure 3 Comparison of function at 90-days of TIMS-China with those in SITS, ECASS III, and CASES.

whether the Western guidelines for intravenous rtPA treatment would be suitable to Asian patients with AIS.

This study abstracted data of intravenous rtPA therapy, which followed Western guideline from the Chinese national thrombolysis registry, TIMS-China. Data showed that there were no significant differences in SICH at 24- to 36-h postintravenous rtPA therapy, or mortality and functional outcomes at day 90 between the 0- to 3-h group and the 3- to 4.5-h group in Chinese patients with AIS. When comparing the outcomes of patients that treated at 3- to 4.5-h window in TIMS-China with those data from three Western studies, the SICH rates, mortalities, and function outcomes were comparable. The results in TIMS-China showed a lower symptomatic intracranial hemorrhage rate, but no obvious change in

mortality, compared with that from ECASS III. These results confirmed that thrombolysis using Western guideline and extended thrombolysis window to 4.5 h are as safe and effective in Chinese patients with AIS as in the Western patients.

The definition of SICH after thrombolysis is still controversial. In this study, we applied different definitions of SICH in comparing the SICH rates between the 0- to 3-h group and 3- to 4.5-h group in the TIMS-China study, and the SICH rates in 3- to 4.5-h groups with three other Western studies. We found no change in results. These data suggest no significant difference in outcome measures among these different methods. This result is similar to ECASS III study. Previous studies reported increased SICH rate when rtPA was given at 3- to 4.5-h window [9,16]. Our data showed no significant difference in SICH between 0- to 3-h and 3- to 4.5-h time windows.

In this study, the favorable functional outcomes (independence and excellent recovery) in the 3- to 4.5-h group were nonsignificantly better than those in the 0- to 3-h group. Further analyzing the data showed that most cases in the 3- to 4.5-h group came from the medical centers with more experienced stroke physicians and better medical facilities. Many thrombolysis cases were supported by multimode image guidance, such as magnetic resonance angiography, diffusion-weighted imaging, and perfusion-weighted imaging.

There are more than 7 million stroke cases each year in China, and approximately 65% of them are ischemic [17]. However, only less than 2% of patients with AIS received thrombolytic therapy.

This is lower than the rate of thrombolysis in Europe [18]. Although this study was not a randomized placebo-controlled trial, and it had potential patient selection bias as mentioned above, it is the first study on safety and outcomes of thrombolysis in Chinese patients with AIS, with special focus on thrombolysis during 3 to 4.5 h after symptom onset. The positive results of this study may promote more Chinese medical centers to extend their thrombolysis time window to 4.5 h. This would help to further increase the thrombolysis rate in China and greatly improve the prognosis in Chinese patients with AIS.

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Conflict of Interest

The authors declare no conflict of interest.

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