

INTRAVENOUS THROMBOLYSIS WITH RT-PA OF DIFFERENT ETIOLOGIC STROKE: A TERTIARY HOSPITAL DATABASE STUDY OVER THREE YEARS

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ABSTRACT

Aim: To investigate the differences in thrombolytic response among various stroke subtypes and related influencing factors.

Materials and methods: Clinical data of 64 AIS patients who received intravenous thrombolysis were collected.

Results: Males, current/former smokers and patients with alcohol consumption history had relatively better prognosis after thrombolysis. Patients in the cardiogenic embolism and Large-artery atherosclerosis subtype groups had poorer prognosis. Logistic Regression Multivariate Analysis on the prognosis of thrombolysis among various stroke subtypes showed better prognosis in CE group than those in the other four subtype groups. The data obtained in the present study only demonstrated no statistically significant differences in thrombolytic effectiveness among various subtype groups.

Conclusion: It was unnecessary to spend too much time on subtype classification of stroke within the time window of emergency thrombolytic therapy. Early thrombolysis would grant more benefit for the patients suspected of presenting cardiogenic stroke.

Key words: Stroke; Thrombolysis; TOAST classification; modified Rankin Scale; Recombinant human tissue-type plasminogen activator

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Background

Up to date, intravenous administration of recombinant human tissue-type plasminogen activator (rt-PA) is the only effective therapeutic regimen proved by evidence-based analysis in the treatment of acute ischemic stroke (AIS) in hyper-acute phase; early and effective thrombolysis plays a determinant role in the reversing ischemic penumbra, as well as reducing the severity of neurologic injuries. With advancements in diagnostic technique and in-depth studies on the pathogenesis of stroke, etiological typing of AIS has been demonstrated to be essential for development of individualized therapy, evaluation of prognosis and determination of effective prophylactic strategy.

Although the current study suggested that there was no subtype-dependent variation in the effectiveness of thrombolysis conducted on patients with AIS and it was unnecessary to spend too much

time on subtype classification⁽¹⁾, investigation of the thrombolytic response among different stroke subtypes and identification of possible influencing factors still have implications in the thrombolytic management and prognostic assessment.

In the present study, clinical data of 64 AIS patients who received thrombolysis in the Department of Neurology at the First People's Hospital Affiliated to Shanghai Jiao Tong University were reviewed, and, through adapting 3-month prognosis as the judging criteria, the variation in intravenous thrombolytic response among different stroke subtypes and the possible risk factors were investigated.

Methods and methods

Patients

Among 69 AIS patients who received intravenous rt-PA thrombolysis in the Department of

Neurology at the First People's Hospital Affiliated to Shanghai Jiao Tong University between January 1st 2010 and December 31st 2012, 64 were enrolled in the present study as 5 were excluded due to incomplete data or lost to follow-up. The clinical data were collected by the same trained neurologist, including gender; age; time of onset; previous medical history; neurological examination, vital signs and baseline NIHSS score on admission; laboratory, electrocardiogram and echocardiographic findings within 30 minutes post admission; findings of cranial imaging (CT or MRI) scan within 30 minutes post admission; time of initiation of thrombolysis; NIHSS score on 24 hour after thrombolysis; and the findings of cranial imaging scan on 24 hour after thrombolysis. These patients' 3-month prognosis was rated by another trained neurologist, by using modified Rankin Scale (mRS). The follow-ups were conducted via out-patient return visit or telephone with either the patient or one of his/her immediate family members (confirmed by another family member). Repeated consultant was done 1 week later (preventing memory bias).

Classification

Diagnosis of acute ischemic stroke was made in accordance with "Guidelines for the early management of adults with ischemic stroke 2007"⁽²⁾. According to TOAST subtype classification system⁽³⁾, cerebral infarction were classified into five etiological subtypes, namely, the Large-artery atherosclerosis (LAA) type, the Small-artery occlusion (SAO) type, the Cardiogenic embolism (CE) type, the Other causes (OC) type, and the undefined causes (UND) type.

The time window of thrombolysis was classified into ≤ 180 min (within 3 hours) group, 181-270 min (3-4.5 hours) group and >270 min (more than 4.5 hours) group. The criteria of prognostic evaluation after thrombolysis were: mRS ≤ 2 was considered as excellent prognosis while mRS >2 was considered poor prognosis (both were measured 90 days post thrombolysis).

Data analysis

The data were documented in an Access database project after being reviewed by two investigators. All the measurement data were expressed in the form of mean \pm standard deviation. Analysis of variance test was employed for inter-group comparison; while χ^2 test was used for rate comparison (Fisher Exact Test was used if $n < 5$) and OR value,

95% CI and P value were obtained. The effects of different stroke subtypes on post-thrombolysis prognosis was analyzed by using Logistic Regression Multivariate Analysis by taking gender, hypertension, diabetes, hyperlipemia, atrial fibrillation, coronary heart disease, smoking, alcohol use, site of infarction, baseline NIHSS score and duration of thrombolysis as the covariant and prognostic rating was the dependent variant. All the analysis took a level of significance at $\alpha = 0.05$. All the data were statistically processed by using SPSS 14.0 and SAS 9.2 software.

Results

Distributions of demographic data in various stroke subtypes

A total of 64 patients met the diagnostic criteria for AIS. There were 44 males (68.75%) and 20 females (31.25%), with a mean age of 61.36 ± 12.10 years. The differences in patient's gender, age, hypertension, atrial fibrillation, coronary heart disease, smoking, alcohol use, site of infarction, symptomatic hemorrhage, duration of thrombolysis and baseline NIHSS score were not statistically significant (Table 1).

Parameters		LAA (n=28)	CE (n=22)	OTHERS (n=14)	P value
Age (years)		60.89 \pm 11.03	65.05 \pm 13.31	56.5 \pm 11.04	0.113
Gender	Male	23(82.14)	11(50)	10(71.43)	0.05
	Female	5(17.86)	11(50)	4(28.57)	
Hypertension		18(64.29)	11(50)	5(35.71)	0.203
Diabetes		6(21.43)	5(22.73)	0(0)	0.155
Atrial fibrillation		0(0)	13(59.09)	0(0)	--
Coronary heart disease		6(21.43)	10(45.45)	4(28.5)	0.185
Smoking		16(57.14)	7(31.82)	7(50)	0.198
Drinking		12(42.86)	3(13.64)	4(28.57)	0.08
Ischemic location	Anterior	22(78.57)	20(90.91)	8(57.14)	0.073
	Posterior	5(17.86)	1(4.55)	6(42.86)	
	Mixed	1(3.57)	1(4.55)	0(0)	
SICH	Yes	2(7.14)	3(13.64)	1(7.14)	0.699
Time to thrombolysis (min)		193.82 \pm 66.47	169.09 \pm 69.33	167.5 \pm 57.2	0.315
Baseline of NIHSS score		13.07 \pm 6.39	13.5 \pm 6.43	10.29 \pm 5.84	0.294

Table 1: Patient characteristics and stroke subtype distribution.

Date were expressed as n (%) or mean \pm S.D.; SICH: symptomatic intracranial hemorrhage; NIHSS: national institutes of health stroke scale; LAA: Large-artery atherosclerosis; CE: Cardioembolism; OTHERS: Small-artery occlusion Lacunar, other determined and undetermined etiology.

Proportion of patients with good prognosis in various stroke subtypes at different thrombolytic time window

In the LAA subtype group, the percentages of patients with $mRS \leq 2$ were 56.3%, 75% and 50% at time windows of ≤ 180 min, 181~270min and >270 min, respectively. In the CE subtype group, the percentages of patients with $mRS \leq 2$ were 50.0% and 60% at time windows of ≤ 180 min and 181-270min, respectively. In the others group, the percentages of patients with $mRS \leq 2$ were 87.5% and 66.7% at time windows of ≤ 180 min and 181-270min, respectively (Figure 1).

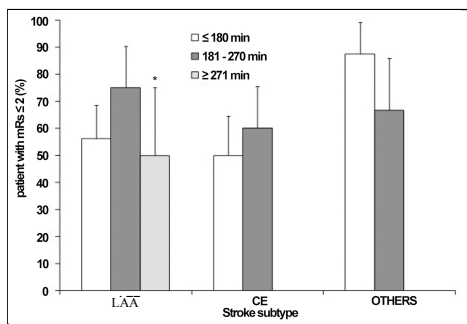


Fig. 1: Outcome on the modified Rankin scale ($mRS \leq 2$) by different stroke subtypes in different treatment time-window. LAA: Large-artery atherosclerosis; CE: Cardioembolism; OTHERS: Small-artery occlusion Lacunar, other determined and undetermined etiology. * There was only LAA subtype cases can be followed up on time-window of outstrip 270 min.

Logistic Univariate Analysis on different influencing factors and various subtypes

From the results of univariate analyses, male patients showed better prognosis after thrombolysis than females (OR, 2.14; 95%CI, 0.73-6.32; $P=0.17$); current/former smokers showed better prognosis than non-smokers (OR, 2.44; 95%CI, 0.85-7.01; $P=0.10$); patients with alcohol consumption showed better prognosis than those without alcohol use (OR, 3.00; 95%CI, 0.86-10.47; $P=0.09$); and the prognosis in other subtype groups were better than those in CE and LAA subtype groups (OR, 2.66; 95%CI, 0.66-10.71; $P=0.17$) (Figure 2).

Logistic Multivariate Analysis on prognosis among different subtype groups

After adjusted for gender, age, hypertension, diabetes, atrial fibrillation, coronary heart disease, smoking, alcohol use, site of infarction, symptomatic intracranial hemorrhage and baseline NIHSS scores, CE group had higher prognostic rating than

the LAA group and the sum of other 3 groups (OR,3.95;95%CI,0.27-57.55; $P=0.32$) (Figure 3).

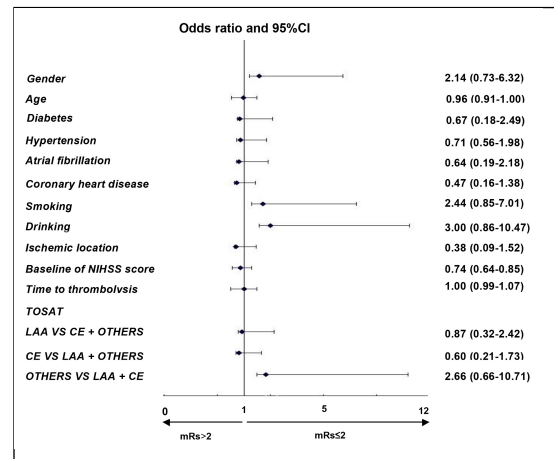


Fig. 2: Univariate analyses of different influencing factors and various subtypes. Male patients showed better prognosis after thrombolysis than females (OR, 2.14; 95%CI, 0.73-6.32; $P=0.17$); current/former smokers showed better prognosis than non-smokers (OR, 2.44; 95%CI, 0.85-7.01; $P=0.10$); patients with alcohol consumption showed better prognosis than those without alcohol use (OR, 3.00; 95%CI, 0.86-10.47; $P=0.09$); and the prognosis in other subtype groups were better than those in CE and LAA subtype groups (OR, 2.66; 95%CI, 0.66-10.71; $P=0.17$).

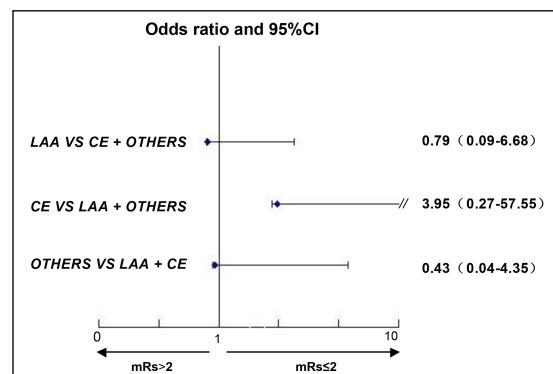


Fig. 3: Comparison of modified Rankin scale at discharge and at three months ($mRS \leq 2$ vs $mRS > 2$) by stroke subtype adjusting for gender, age, hypertension, diabetes, atrial fibrillation, coronary heart disease, smoking, drinking, ischemic location, symptomatic intracranial hemorrhage, time to thrombolysis and baseline of NIHSS score. LAA: Large-artery atherosclerosis; CE: Cardioembolism; OTHERS: Small-artery occlusion Lacunar, other determined and undetermined etiology.

Discussion

For the treatment and prevention of ischemic stroke, scientifically reasonable etiological typing had many clinical implications. Currently, the most

recognized and widely-accepted classification system was the TOAST subtype classification system. Further AIS subtyping according to TOAST classification has been proved to facilitate the establishment of prevention/treatment strategy, as well as to improve risk/benefit ratio.

Currently, it is generally believed that the efficacy of intravenous rt-PA is similar within 3 hours^(4, 5). Therefore, spending time on etiological classification for patients with acute ischemic stroke seems to be unnecessary as it may delay the best treatment timing⁽¹⁾. However, there is indeed variation in both short-term and long-term efficacies for thrombolytic therapy conducted on patients with different AIS subtypes. Therefore, retrospective analysis on the prognostic characteristics and influencing factors of thrombolysis in the treatment of various stroke subtypes without delaying the best treatment timing still had great clinical implications.

In the present study, clinical data obtained from 64 serial AIS patients who received intravenous rt-PA therapy in our center were analyzed retrospectively; all of these patients had complete diagnosis and post-treatment subtype classification, in combination with follow-ups; and the prognostic features of various subtypes were investigated.

From data analysis, three subtype (SOA, OC and UND) groups had higher percentage of patients with excellent prognosis after receiving thrombolysis within 180 min time window than the LAA and CE subtype groups. Although the clinical features and factors appeared to be evenly distributed among the various subtypes, the follow-up data still showed differences when compared the other three groups with the LAA and CE groups, as the three groups had relatively younger mean age, smaller percentages of patients with cerebrovascular disease risk factors, lower baseline NIHSS score and shorter thrombolysis time window. All of these differences may contribute to more benefit from thrombolytic therapy. Therefore, it was inappropriate to totally attribute the differences in prognosis to different subtypes.

The results of univariate analysis on different risk factors showed that males had better thrombolytic outcomes than females. Several previous studies have demonstrated higher severity of stroke occurred in females than in males^(6, 7); however, other factors (e.g. delayed pre-admission transport, delayed post-admission diagnosis and treatment) may also probably contribute to the poorer prognosis in females when compared with males.

Through analysis on our follow-up data, there was no statistically significant difference in baseline NIHSS scores (12.02 ± 6.33 VS 13.90 ± 6.26 ; $P=0.91$) and thrombolysis time window (174.70 ± 63.99 min VS 190.25 ± 70.16 min; $P=0.50$) between the two genders, although there was a higher tendency of delayed treatment for females.

With regard to the better prognosis for current/former smokers, several studies have demonstrated improved prognosis for patients with acute myocardial infarction and received intravenous thrombolysis⁽⁸⁻¹⁰⁾. The possible mechanism may due to the pro-activation effects of the main constituents in cigarette on the endogenous fibrinolytic system, as well as the increased sensitivity to thrombolytic drugs^(11, 12). Smoker's Parado phenomenon (i.e. smoking was an independent risk factor for improved prognosis of thrombolysis) has also been reported in several studies on AIS⁽¹³⁾. Such phenomenon was also demonstrated in the present study.

The data showed a 2.44-fold increase in the numbers of patients with excellent prognosis in smokers than in non-smokers. In addition, the data of present study suggested a better prognosis in patients with alcohol consumption than non-alcoholic patients; a phenomenon has never been reported. In our follow-up data, we found that 18 of 19 patients with alcohol use were alcoholic smokers (94.7%). Therefore, we deduced that better prognosis achieved by alcohol users may largely be attributed to smoking, a definitive risk factor. Further larger subtyping-classificatory studies were required to confirm whether alcohol consumption was one of the independent risk factor for improved thrombolytic prognosis.

In regard to assessment on thrombolytic prognosis for different stroke subtypes, NINDS study has demonstrated better thrombolytic prognosis achieved by patients with SAO subtype stroke than those with other subtypes, such result was in consistency with the previous study conducted by Hisa⁽¹⁾. In contrast, the study conducted by Rocha and his colleagues⁽¹⁴⁾ suggested that the differences in early thrombolytic prognosis (within 24 hours and on discharge) between CE subtype and the other subtype were not statistically significant, but the CE appeared to have better long-term response (after 3 months) than other subtypes.

From univariate analysis conducted in the present study, the prognosis achieved by the LAA and the CE subtype groups were slightly better than the other subtype groups, although there was no statis-

tically significant differences in thrombolytic prognosis among various subtypes. This has never been reported in published literatures. We considered it was most likely to be attributed to specific characteristics in the follow-up data. In the present study, the other subtypes (including SAO, OC and UND) had fewer cerebrovascular disease risk factors, lower NIHSS scores and lower mean ages than the LAA and CE groups, and thus leading to larger possibility of acquiring more post-thrombolysis benefits.

After adjusted for gender, age, hypertension, diabetes, atrial fibrillation, coronary heart disease, smoking, alcohol use, site of infarction, symptomatic intracranial hemorrhage and baseline NIHSS scores, Logistic Regression Multivariate Analysis on the prognosis of thrombolysis among various stroke subtypes showed better prognosis in CE group than those in the other four subtype groups. The percentage of patients acquired excellent prognosis was 3.95-fold higher than those of the LAA and OC groups. Such prognostic outcome was similar to the results of 3-month follow study conducted by Rocha. But the difference in the present study was not statistically significant due to limited number of cases enrolled.

Currently, it was commonly believed that emboli in CE subtype stroke were different in constituents when compared with those in other subtypes. Cardiogenic emboli were usually reddish, softer emboli sensitive to thrombolytic drugs; and such emboli also featured spontaneous disintegration and higher recanalization rate. Prompt thrombolysis prior to the formation of white emboli may bring more benefits for patients with CE subtype stroke.

Conclusions

In conclusion, at the moment, there is no sufficient evidence to support the existence of significant differences in prognosis among various subtypes, which are in consistent with other reported results. Therefore, it is still not recommended to perform etiological subtype classification for stroke prior to thrombolysis. Further large-scale studies are required to verify the better long-term prognosis in patients with CE subtype stroke than those with other subtypes. However, we still recommend early thrombolysis for patients suspected of presenting cardiogenic stroke, as early therapy is more likely to grant more benefits.

It was unnecessary to spend too much time on subtype classification of stroke within the time window of emergency thrombolytic therapy. Early thrombolysis would grant more benefit for the patients suspected of presenting cardiogenic stroke.

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