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Original Article

Thrombolysis lead to better long-term outcome in Chinese stroke patients

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ABSTRACT

Aim: The rate of thrombolysis in Chinese acute ischemic stroke (AIS) was low and little was known about the long-term outcome. We aimed to compare the prognosis between thrombolysis and ordinary anti-platelet strategies in AIS. **Methods:** Patients, who were consecutively registered in our hospital from January 2005 to June 2012, were retrospectively studied. Inclusion criteria: (1) primary diagnoses of cerebral infarction coded with implantable cardioverter defibrillator-10 I63 to I69; (2) symptoms onset to treatment time (OTT) within 6 h; (3) thrombolysis with alteplase (TROM) or ordinary anti-platelet therapy (ANTP). Exclusion criteria: (1) symptoms and signs diminished rapidly without apparent neurological deficits; (2) no visible lesions on diffusion weighted image in magnetic resonance imaging; (3) cerebral infarction caused by serious metabolic in-balance or infections. The endpoints were defined as favorable (modified Rankin Scale 0-2) or being survival. Proportions of favorable outcome or survival were estimated by Kaplan-Meier curve and Cox regression. **Results:** One hundred and sixty eight cases were analyzed. Ninety one were in TROM and 77 in ANTP. Male accounted for 82 (48.8%) and female 86 (51.2%). The median of age was 74 [interquartile range (IQR) 67-79], national institute of health stroke scale (NIHSS 9) (IQR 5-17) and OTT 3.9 h (IQR 3.0-4.8) respectively. The median length of follow-up was 112 (IQR 63.4-163.8) weeks. By the end of December 31, 2012, 87 patients (51.8%) reached favorable outcome while 81 (48.2%) unfavorable. Forty five (26.8%) cases deceased. Kaplan-Meier curve estimation showed a longer favorable period of time in TROM than those in ANTP (212 weeks 95% confidence interval (CI) 169.5-254.5 *vs.* 126.9 weeks 95% CI 105.2-148.6; Log-Rank test $x^2 = 19.632$, $P = 0.000$), while no significance was seen in survival time (258.0 weeks 95% CI 231.5-284.5 *vs.* 160.8 weeks 95% CI 153.0-168.5; Log-Rank test $x^2 = 2.427$, $P = 0.119$). In Cox regression, thrombolysis showed an independent protective effect for longer period of favorable outcome [202 *vs.* 151 weeks, $P = 0.026$, heart rate (HR) 1.96, 95% CI 1.958-3.540] and longer survival time instead (333 *vs.* 170 weeks, $P = 0.000$, HR 4.322, 95% CI 1.942-9.618). The estimated proportion of favorable outcome in Chinese urban AIS was about 91% for 1 year and 50% for about 3.4 years, while the estimated proportion of survival was about 98.5% for 1 year and 50% for about 5.3 years, respectively. **Conclusion:** Chinese urban AIS patients who underwent thrombolysis with alteplase might have a better long-term outcome than those receiving ordinary anti-platelet therapy.

Key words: Stroke; thrombolytic therapy; Chinese; alteplase; Cox regression

INTRODUCTION

Thrombolysis with alteplase had been proven to be most effective in acute ischemic stroke (AIS) and its long-term good effects were verified by the Third International Stroke Trial 3.[1] In China the rate of thrombolysis of AIS was low, perhaps due to the fear of bleeding or conceptions of no need to treat mild stroke.[2] There is still no controlled study concerning the long-term outcome in Chinese AIS. Even in patients with lacunar infarction, which account for nearly

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Table 1: Main differences of variables between thrombolysis and anti-platelet groups

Variables	TROM (n = 91)	ANTP (n = 77)	Z/x^2	P value
Demographics				
Gender (male), n (%)	39 (23.2)	43 (25.6)	2.815	0.121
Age (years), median (IQR)*	72 (14)	76 (12)	-2.779	0.005
Length (w), median (IQR)*	149.6 (140.9)	90.7 (69.6)	-3.463	0.001
OTT (h), median (IQR)	3.7 (1.5)	4.2 (2.2)	-1.855	0.064
Vital signs				
NIHSS Scale, median (IQR)*	13 (11)	5 (5)	-7.443	0.000
BT (℃), median (IQR)	36.5 (0.6)	36.5 (0.5)	-0.140	0.889
HR (/min), median (IQR)	80 (19)	80 (18)	-0.151	0.880
BPS (mmHg), median (IQR)	154 (35)	150 (41)	-0.997	0.319
BPD (mmHg), median (IQR)	85 (21)	80 (21)	-1.951	0.051
Laboratory tests				
WBC (×10^9/L), median (IQR)	8.66 (3.98)	8.77 (2.27)	-0.347	0.729
PLT (×10^9/L), median (IQR)	218.00 (68.00)	206.70 (65.00)	-0.275	0.783
HCT, median (IQR)	0.39 (0.05)	0.38 (0.08)	-1.653	0.098
INR, median (IQR)	1.02 (0.21)	1.06 (0.11)	-1.132	0.258
APTT (s), median (IQR)	34.40 (5.60)	34.90 (4.53)	-0.939	0.348
FIB (g/L), median (IQR)	3.45 (1.09)	3.45 (0.92)	-1.187	0.235
Hs-CRP (mg/L), median (IQR)	11.33 (17.99)	10.37 (20.01)	-0.672	0.502
GLU (mmol/L),median (IQR)	7.70 (3.40)	7.84 (1.84)	-0.624	0.533
Bicarbonate (mmol/L), median (IQR)	23.50 (3.50)	23.17 (2.40)	-0.178	0.858
TG (mmol/L), median (IQR)	1.05 (0.67)	1.04 (0.71)	-0.516	0.606
CH (mmol/L), median (IQR)	5.04 (1.57)	4.95 (1.11)	-0.196	0.845
TPR (mg/L), median (IQR)*	0.04 (0.17)	0.14 (0.30)	-2.237	0.025
TP (g/L), median (IQR)	64.20 (8.50)	62.73 (5.50)	-1.565	0.118
ALT (iu/L), median (IQR)	19.00 (10.00)	19.48 (9.39)	-0.105	0.916
CR (mmol/L), median (IQR)	80.00 (33.50)	87.00 (33.35)	-1.004	0.315
TOAST classifications				
Atherosclerotic, n (%)	63 (37.5)	56 (33.3)		
Cardiac embolism, n (%)	22 (13.1)	17 (10.1)	0.288	0.866
Small artery, n (%)	6 (3.6)	4 (2.4)		
OCSP classifications*				
Total anterior, n (%)	18 (10.7)	4 (2.4)		
Partial anterior, n (%)	49 (29.2)	48 (28.6)		
Posterior, n (%)	16 (9.5)	18 (10.7)	7.993	0.046
Lacunar, n (%)	8 (4.8)	7 (4.2)		
Hemorrhagic transformations*				
None, n (%)	70 (41.7)	74 (44.0)		
Hemorrhagic Infarction, n (%)	9 (5.4)	3 (1.8)	14.042	0.001
Parenchymal, n (%)	12 (7.1)	0 (0)		
Risk factors				
Hypertension, n (%)*	64 (38.1)	42 (25.0)	4.463	0.038
Diabetes, n (%)	23 (13.7)	17 (10.1)	0.235	0.717
Heart arrhythmia, n (%)*	20 (11.9)	6 (3.6)	6.416	0.017
Heart failure, n (%)*	29 (17.3)	9 (5.4)	9.704	0.003
Smoking, n (%)	24 (14.3)	26 (15.5)	1.090	0.314
Stroke history, n (%)	19 (11.3)	13 (7.7)	0.432	0.559
Family history of stroke, n (%)*	7 (4.2)	0 (0)	6.181	0.016
Outcome				
Favorable, n (%)	44 (26.2)	43 (25.6)	0.938	0.356
Deceased, n (%)	30 (17.9)	15 (8.9)	3.868	0.056

*P < 0.05 (two tailed); TROM: thrombolysis group; ANTP: anti-platelet group; OTT: onset to treatment time; IQR: interquartile range; NIHSS: national institute of health stroke scale; BT: body temperature; HR: heart rate; BPS: systolic blood pressure; BPD: diastolic blood pressure; WBC: white blood cell count; PLT: platelet count; HCT: hematocrit; INR: international normalized ratio; APTT: activated partial thromboplastin time; FIB: fibrinogen; hs-CRP: high sensitivity C reactive protein; GLU: blood glucose; TG: triglyceride; CH: total cholesterol; TRP: troponin; TP: total protein; ALT: aminotransferase; CR: serum creatinine

37% of total AIS and supposed to be "mild", did not reach a favorable end.[3] We aimed to compare the prognosis between thrombolysis and ordinary anti-platelet strategies in Chinese AIS.

METHODS

Our hospital is one of the tertiary teaching institute attached to the Guangzhou Medical University, which is financed by government and located in the central downtown of Guangzhou city, having a total of 1,200 beds and supplies emergency medical services covering 1.5 million residents and admits more than 500 documented stroke patients each year. The number of inhabitants in the city has exceeded 12 million. One of the authors (LN) was ever a collaborator of the imaging-based thrombolysis trial in acute ischemic stroke-II.[4]

We searched the patients who had been consecutively registered in our database from January 2005 to June 2012.

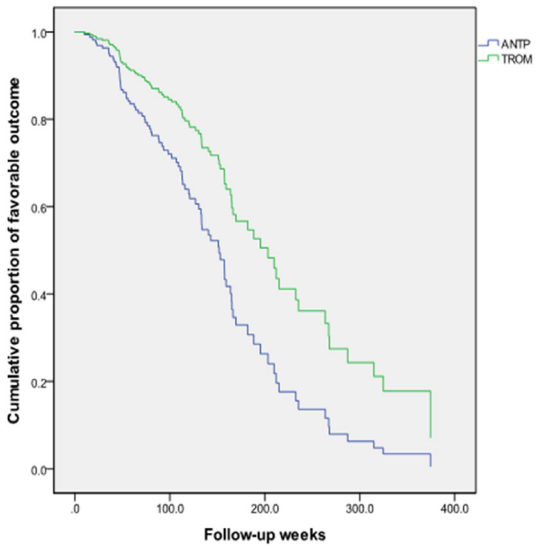

Figure 1: Cox regression. Estimation of favorable outcome proportions between TROM and ANTP. TROM: thrombolysis group; ANTP: anti-platelet group; $P = 0.026$

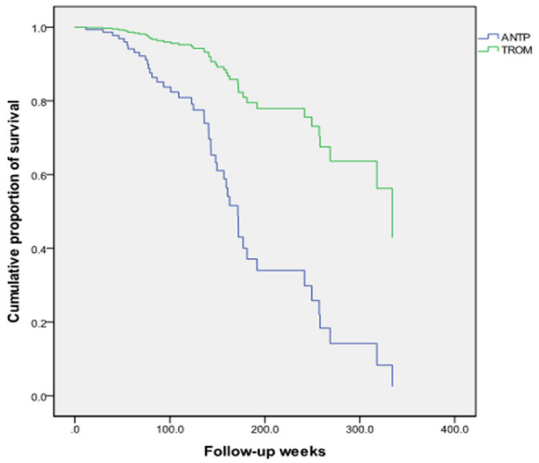

Figure 2: Cox regressions. Estimation of survival proportions between TROM and ANTP. TROM: thrombolysis group; ANTP: anti-platelet group; $P = 0.000$

The survey was approved by The Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University. The inclusion criteria were the following: (1) primary diagnoses of cerebral infarction coded with International Classification of Diseases 10th edition I63 to I69; (2) symptoms onset to treatment time was within 6 h; (3) thrombolysis with alteplase as per NINDS trial protocol or ordinary anti-platelet therapy such as aspirin and clopidegrel. Exclusion criteria included: (1) symptoms and signs diminished rapidly without apparent neurological deficits; (2) no visible lesions on diffusion weighted image in magnetic resonance imaging; (3) cerebral infarction caused by serious metabolic in-balance or infections. Patients were divided into thrombolysis group and ordinary anti-platelet one. The endpoints were defined as favorable (modified Rankin Scale 0-2) or survival. Follow-up were conducted through December, 2012 by structured telephone interview.

Data for variables nearest to the time point of treatment were collected using Microsoft® Office Excel 2003 (Microsoft Corporation, Redmond, WA, USA). The variables included demographics, vital signs, laboratory tests and radiological manifestations. Known risk factors such as cardiac abnormalities, hypertension and diabetes, smoking and prior stroke were included. The time elapse before treatment was recorded. National Institute of Health Stroke Scale (NIHSS) scores were recorded in documents and reviewed by an author (WY) who had passed the NIHSS training course in 2009.

Statistical analysis

For baseline independent variables, quantitative missing values were replaced by linear regression estimates. We used binary correlations to test the collinearities of independent variables and made combinations or reductions under professional considerations. Differences between groups were tested by Mann-Whitney *U*-test, Pearson chi-square and Fisher's exact test. In Kaplan-Meier curve estimation and Cox regression, log rank test and backward step-wise likelihood chi-square test were used respectively. The inclusion and exclusion criterion of stepping probability was 0.05 and 0.10 respectively. $\alpha = 0.05$ (two sided) was considered significant. Data were calculated by IBM® SPSS® statistics version 19.

RESULTS

Of the 2,949 AIS patients screened, one hundred and eighty three met the inclusion and exclusion criteria. Fifteen patients lost follow-up. One hundred and sixty eight individuals entered the final analyses. Ninety one were included in thrombolysis group (TROM) and 77 in anti-platelet (ANTP) one. Male accounted for 82 (48.8%) and female 86 (51.2%). The median of age was 74 [interquartile range (IQR) 67-79], NIHSS 9 (IQR 5-17) and onset to treatment time 3.9 h (IQR 3.0-4.8) respectively. The median length of follow-up was 112 (IQR 63.4-163.8) weeks. Differences of variables between two groups were listed in Table 1. Patients in TROM were younger, had higher NIHSS scales and lower serum troponin level, higher proportion of total anterior cerebral infarction, more hemorrhagic transformations and higher proportions of hypertension, heart abnormalities and family history of stroke. By the end of December 31, 2012, 87 patients (51.8%) reached favorable outcome while 81 (48.2%) unfavorable. Death occurred in 45 (26.8%) cases. No significant differences were detected between TROM and ANTP. In Kaplan-Meier curve estimation, patients in TROM showed a longer favorable period of time than those in ANTP [212 weeks 95% CI 169.5-254.5 *vs.* 126.9 weeks 95% confidence interval (CI) 105.2-148.6; Log-Rank test $x^2 = 19.632$, $P = 0.000$], while no significance was seen in survival time (258.0 weeks 95% CI 231.5-284.5 *vs.* 160.8 weeks 95% CI 153.0-168.5; Log-Rank test $x^2 = 2.427$, $P = 0.119$). After adjusting covariates of age, gender

and NIHSS, international normalized ratio, high sensitivity C reactive protein, heart failure, diabetes and interaction of NIHSS and thrombolysis in Cox regression, thrombolysis in AIS showed an independent protective effect for longer period of favorable outcome [202 *vs.* 151 weeks, $P = 0.026$, heart rate (HR) 1.96, 95% CI 1.958-3.540]. While adjusted for factors of white blood cell count, onset to treatment time and serum bicarbonate level, serum creatinine level and interaction of NIHSS and white blood cell count additionally, thrombolysis itself might be an independent predictor for longer survival instead (333 *vs.* 170 weeks, $P = 0.000$, HR 4.322, 95% CI 1.942-9.618) [Figures 1 and 2]. The estimated proportion of favorable outcome was about 91% for 1 year and 50% for about 3.4 years (4.2 *vs.* 3.1), while the estimated proportion of survival was about 98.5% for 1 year and 50% for about 5.3 years (6.9 *vs.* 3.5).

DISCUSSION

In this hospital-based retrospective cohort study, we found thrombolysis with alteplase might have a protective effect for longer period of time of favorable outcome and survival in Chinese AIS patients. To our knowledge, this is the first observational survey that compared the long-term prognoses of thrombolysis and anti-platelet therapy in mainland China. The overall estimated five-year survival rate was 50%, comparable to published data.[5] Wang *et al.*[6] found one-year survival rate of hospitalized AIS patients was about 89.2% in west China, much lower than that one in our cohort (98.5%). This may due to the fact that they enrolled patients with symptoms onset within 14 days. Much of them might not have received timely thrombolytic or anti-platelet therapies. With time elapsed, stroke might progress and leading to a worse end. Notably, much of patients in their data set were mild stroke (median NIHSS score 5) with high proportion of small artery occlusion (42.9%), while we enrolled more severe patients (median NIHSS score 9) with 70.8% large artery occlusion sub-type. These results might remind the importance of timely and fully managements of mild stroke, which is more common in Chinese population with unfavorable outcome,[3,7] to reach a longer survival.

Compared to that of Gensicke *et al.*[8] in Switzerland, Chinese AIS patients received thrombolytic therapy seemed to have longer 50% survival time (6.9 *vs.* 4.0 years) and good outcome (4.2 *vs.* 3.0 years). We cannot make a conclusion due to the disparities of pre-defined endpoint (mRs 0-1 in Swiss *vs.* 0-2 in CHN) but the stroke severity was comparable (NIHSS 13 *vs.*14), which had been proven to be the most important determinant of stroke mortality.[9] Although Asian ethnic patients in US had higher mortality rate in hospital stay after thrombolysis,[10] and we too previously reported a higher 3-month mortality rate of 18%[11] than that in western countries,[12] further study should be performed to clarity the potential benefits of thrombolysis for long-term survival in Chinese patients, with prospective design and less bias.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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