Original Article

Is Low Dose of Rt-PA Treatment Effective in Acute Ischemic Stroke? A Comparison Study with the Standard Dose

Vorasoot N, MD[1,2], Boonpayak S, MD[1,2], Kongbunkiat K, MD[1,2], Kasemsap N, MD[1,2], Tiamkao S, MD[1,2], Sawanyawisuth K, MD, PhD[1,3]

[1] Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand
[2] North-Eastern Stroke Research Group, Khon Kaen University, Khon Kaen, Thailand
[3] Sleep Apnea Research Group, Research Center in Back, Neck and Other Joint Pain and Human Performance, Research and Training Center for Enhancing Quality of Life of Working Age People and Research and Diagnostic Center for Emerging Infectious Diseases (RCEID), Khon Kaen University, Khon Kaen, Thailand

A recombinant tissue plasminogen activator (rt-PA) treatment is effective in acute ischemic stroke. Treatment dosage of the rt-PA in Asian populations is still debating. The present study therefore aimed to evaluate the efficacy and side effects of the low dose treatment of rt-PA in Thai acute ischemic stroke patients compared with the standard dose. The authors conducted a multicenter descriptive retrospective analytical study in three hospitals in northeastern, Thailand. The inclusion criteria were acute ischemic stroke patients registered in the Stroke Fast Track treatment for those over the age over 18 years and received the rt-PA treatment. All eligible patients were divided into two groups by dose of rt-PA treatment; low dose with 0.6 mg/kg of rt-PA and standard dose or 0.9 mg/kg. Baseline characteristics and stroke outcomes of all patients were recorded. The stroke outcomes included the NIH Stroke Scale (NIHSS), side effects of rt-PA, and deaths. There were 371 patients met the study criteria and categorized as low dose group for 117 patients (31.54%) and standard dose group for 254 patients (68.46%). The low dose group had older age (67.5 vs. 60.1 years), higher proportions of atrial fibrillation (23.1% vs. 11.8%), and baseline NIHSS (12 vs. 9) than the standard dose group. Regarding outcomes or complications, there was no significant different of any outcomes between both groups such as NIHSS improvement, intracerebral hemorrhage, or mortality. In conclusion, the low dose of rt-PA treatment for acute ischemic stroke may be justified particularly those with older age or more severe stroke.

Keywords: Age, Atrial fibrillation, NIHSS

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Acute ischemic stroke is a common disease in clinical practice causing disability and deaths worldwide[1,2]. The mainstay of treatment is thrombolytic therapy or recombinant tissue plasminogen activator (rt-PA). If given within 4.5 hours after stroke onset, the stroke outcomes are significantly improved with lower mortality rate[3-6]. In northeastern Thailand, the stroke fast track has established for years and rt-PA is recommended in suitable cases.

The standard dose for rt-PA is 0.9 mg/kg which provides the good outcome for acute ischemic stroke. However, there are some serious side effects from the rt-PA including major organ bleeding or deaths[7]. Responses to the rt-PA treatment are varied particularly by ethnicity; Japanese patients may have better responses than Caucasians or African-American patients[8-11]. In Japan, using low dose of rt-PA or 0.6 mg/kg had comparable stroke outcomes as 0.9 mg/kg[12-14]. These data were different from the East Asia which found that the standard dose of rt-PA had better outcome than the low dose[15]. There is limited study in this issue in Thai patients. The present study therefore aimed to evaluate the efficacy and side effects of the low dose treatment of rt-PA in Thai acute ischemic stroke patients compared with the standard dose.

Correspondence to:

Sawanyawisuth K.

Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.

Phone: +66-43-363664, **Fax:** +66-43-348399

E-mail: kittisak@kku.ac.th

Materials and Methods

The present study was a multicenter descriptive retrospective analytical study. The inclusion criteria were acute ischemic stroke patients registered in the Stroke Fast Track treatment for those over the age over 18 years and received the rt-PA treatment. Those patients with had incomplete data or loss to follow-up were excluded. The study sites included three provincial hospitals in the northeastern Thailand; Srinagarind or Khon Kaen University Hospital, Chaiyaphum Hospital, and Kalasin Hospital. The study period was between January 1st, 2010 and December 31st, 2012.

All eligible patients were divided into two groups by dose of rt-PA treatment; low dose with 0.6 mg/kg of rt-PA and standard dose or 0.9 mg/kg. Baseline characteristics and stroke outcomes of all patients were recorded. The stroke outcomes included the NIH Stroke Scale (NIHSS), side effects

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of rt-PA, and deaths. All outcomes were evaluated at discharge date.

Sample size calculation and statistical analysis

Based on the previous study[12], the improvement of neurological symptoms was 33.1% in low dose and 47.2% in high dose of rt-PA treatment. The required sample size for confidence of 95% and power of 80% was 190. Studied variables and outcomes between both study groups were compared by descriptive statistics. All statistical analyses were computed by the STATA software version 10.0 (College Station, Texas, USA).

Results

During the study period, there were 434 patients met the study criteria. Of those, 63 patients (14.5%) were excluded due to incomplete data. In total, there were 371 patients for analysis and categorized as low dose group for 117 patients (31.54%) and standard dose group for 254 patients (68.46%). There were eight significant different factors between both groups (Table 1) including age, history of hypertension/heart failure/or atrial fibrillation, history of lipid lowering agent use, onset to needle time, Glasgow coma score, and baseline NIHSS. The low dose group had older age (67.5 vs. 60.1 years), higher proportions of hypertension, heart failure, or atrial fibrillation, longer time from onset to needle time (204 vs. 176 minutes), and baseline NIHSS (12 vs. 9) than the standard dose group.

Regarding outcomes or complications, there was no significant difference in any items between both groups (Table 2). At discharge, the NIHSS improvement proportion was slightly higher in the low dose group than the standard

Table 1. Baseline characteristics of acute ischemic stroke patients receiving an rt-PA treatment categorized by dose of the rt-PA as low or standard dose

Factors	Low dose (n = 117)	Standard dose (n = 254)	*p*-value
Age (years)	67.5±12.7	60.1±19.7	<0.001
Sex (Male)	54 (46.2%)	120 (47.2%)	0.911
BW (kilogram)	60.4±12.0	57.9±21.5	0.307
Underlying disease, n (%)			
Hypertension	72 (61.5%)	113 (44.55)	0.003
Dyslipidemia	23 (19.7%)	43 (17%)	0.560
Diabetes mellitus	31 (26.5%)	59 (23.3%)	0.517
Coronary artery disease	12 (10.3%)	16 (6.3%)	0.206
History of congestive heart failure	8 (6.4%)	2 (0.8%)	0.002
Atrial fibrillation	27 (23.1%)	30 (11.8%)	0.008
Valvular heart disease	10 (8.6%)	14 (5.5%)	0.267
History of PAD	1 (0.9%)	1 (0.4%)	0.533
History of transient ischemic stroke	4 (3.4%)	13 (5.1%)	0.598
Previous stroke	9 (7.7%)	15 (5.95)	0.505
Current smoking	20 (42.6%)	52 (53.6%)	0.286
Current alcohol use	22 (44.9%)	55 (59.8%)	0.111
Previous use of anti-platelet drug	34 (33.3%)	50 (35.2%)	0.125
Previous use of anticoagulant drug	4 (4.0%)	6 (4.9%)	0.499
Previous use of lipid lowering agents	26 (26.2%)	48 (33.6%)	0.043
Onset to needle time (minute)	204±75	176±64	0.002
Glasgow coma score (point)			<0.001
Median	11	15	
Range	3 to 15	7 to 15	
Baseline NIHSS			<0.001
Median	12	9	
Range	1 to 34	1 to 30	
Blood pressure			
Systolic (mmHg)	149±39	149±29	0.354
Diastolic (mmHg)	83±27	84±16	0.505
Plasma glucose (mg/dL)	89±96	108±90	0.054
Creatinine (mg/dL)	0.14±9.26	0.7±6.46	0.627
Cholesterol (mg/dL)	179.4±76.3	184.0±71.9	0.892
Triglyceride (mg/dL)	96.5±132.2	111.0±112.4	0.138
LDL (mg/dL)	91.9±80.1	94.4±82.7	0.830
HDL (mg/dL)	22.8±52.0	28.3±49.6	0.506

Data presented as number (percentage) or mean ± SD, unless indicated otherwise; PAD = peripheral artery disease; LDL = low density lipoprotein; HDL = high density lipoprotein; NIHSS = the NIH Stroke Scale

Table 2. Stroke outcomes and complications of acute ischemic stroke patients receiving an rt-PA treatment categorized by dose of the rt-PA as low or standard dose

Outcomes	Low dose (n = 117)	Standard dose (n = 254)	*p*-value
NIHSS improvement at 24 hr	51 (43.6%)	130 (51.2%)	0.182
NIHSS improvement before dischange	71 (64.6%)	149 (64.2%)	0.999
Intracerebral hemorrhage	14 (14.0%)	21 (18.3%)	0.474
Other bleedings	6 (6.1%)	4 (3.3%)	0.348
Massive infarction	6 (6.1%)	7 (5.7%)	1
Hospital admission day	7.2±16.3	6.3±7.7	0.269
Death	6 (6.1%)	11 (8.9%)	0.613

Data presented as number (percentage) except mean ± SD for hospital admission day

dose group (64.6% vs. 64.2%; *p*-value = 0.999), while the mortality rate was slightly higher in the standard dose group than the low dose group (8.9% vs. 6.1%; *p*-value = 0.613).

Discussion

The present study confirmed the results the previous study from Japan that low dose rt-PA treatment was effective and safe[12]. The percentage of patients with NIHSS improvement in the present study was comparable with the previous study (43.6% vs. 49.5%), while the risk of intracerebral hemorrhage was higher in the present study than the Japanese study (14.0% vs. 5.8%). In the present study, all patients with intracerebral hemorrhage after rt-PA treatment were recorded, but only symptomatic intracerebral hemorrhage patients were reported in the previous study. Therefore, the percentage of reported intracerebral hemorrhage in the present study was higher. Regarding mortality after low-dose rt-PA treatment, the mortality rate in the present study was slightly lower than the Japanese study (6.1% vs. 9.7%) due to different evaluation period. The present study evaluated mortality rate at discharge, while another study recorded mortality rate at three months which might be slightly higher.

The results of the present study may be different from the systematic review from India[15]. The low dose treatment of rt-PA in this study showed better benefit on percentage of NIHSS improvement than the systemic review (43.6% vs. 33.1%), but higher intracerebral hemorrhage (14.0% vs. 3.5%) and lower mortality rate (6.1% vs. 13.1%). The reasons behind these findings may be similar as previously discussed above. Note that both this study and previous systematic review had different baseline characters between those received low and standard dose of rt-PA treatment[15]. The low dose group had older age (67.5 vs. 60.1 years; *p*-value <0.001), higher risks for embolic stroke (23.1% vs. 11.8%; *p*-value = 0.008), and more severe stroke (NIHSS 12 vs. 9; *p*-value <0.001) than the standard dose group. Taken into account for both efficacy and side effects, low dose of rt-PA treatment for acute ischemic stroke may be justified particularly those with older age or more severe stroke.

The present study had some limitations. First, there was no randomization resulting in different baseline characters (Table 1). Second, there may have been a selection bias from an attending physician for dose selection. Finally, the sample size was small. Therefore, larger sample size with a randomized controlled trial may be needed.

What is already known on this topic?

A low dose of rt-PA treatment for acute ischemic stroke is still debating.

What this study adds?

A low dose of rt-PA treatment for acute ischemic stroke may be justified particularly regarding those who are older or suffer more severe strokes.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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