

## Stroke outcomes in Thai elderly patients treated with and without intravenous thrombolysis

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### Abstract

Higher mortality was found in very old patients with acute ischemic stroke treated with intravenous recombinant tissue-plasminogen activator (rtPA) as compared to younger patients. The benefit of thrombolytic treatment in this particular subgroup is still a subject of debate. The purpose of this study was to compare stroke outcomes in Thai patients aged over 70 years treated with and without intravenous rtPA. This was a retrospective review of sequential cases and was not a randomized controlled study. One-hundred and five patients with acute ischemic stroke aged over 70 years who were treated with intravenous rtPA and 105 patients without rtPA treatment (control group) were included in the study. Patients' base-line characteristics and study outcomes of interest were compared. There were significant differences in the base-line characteristics of the two groups. However, for the subgroup of patients aged over 80 years, these characteristics were similar. Those who were treated with intravenous rtPA had a higher rate of favorable outcomes (40% vs 16%; P=0.137) and a lower rate of mortality (22% vs 44%; P=0.128) than patients who did not receive rtPA treatment. In well-matched subgroups of patients aged over 80 years, our retrospective review revealed there was a trend of a higher rate of favorable outcome and lower mortality in patients receiving rtPA treatment. More study is needed to further confirm the suggested benefit of thrombolysis in Asian octogenarian acute stroke patients.

### Introduction

Although intravenous thrombolysis has become a standard treatment for acute

ischemic stroke in eligible patients, the recommendations for treating patients aged over 80 years are still a subject of debate. Many studies have revealed a higher mortality rate and lower favorable outcome rate in patients aged over 80 years. In some studies, the rate of symptomatic intracerebral hemorrhage (ICH) was higher in patients aged over 80 years while in others it was similar to that observed in younger patients.<sup>1-6</sup> However, a large study and a meta-analysis have both recently shown that older patients benefit from treatment at least as much as younger patients.<sup>7,8</sup>

Most of the data are from Western countries. Menon *et al.* assessed risk score for intracranial hemorrhage after intravenous thrombolytic treatment in 10,242 patients with acute ischemic stroke and found that Asian race was one of the independent risk predictors.<sup>9</sup> Data in Asian patients may be different from that in Western populations. Thrombolytic studies from some Asian countries, such as Taiwan and Vietnam, have not included patients aged over 80 years.<sup>10,11</sup> Previous studies in Thai patients showed that older age ( $\geq 70$  years old) was inversely associated with early improvement. Significantly higher rates of mortality and symptomatic ICH were also found in patients aged 70 years or over as compared with younger patients after treatment with recombinant tissue-plasminogen activator (rtPA).<sup>12,13</sup> However, whether treatment with thrombolysis will have a greater beneficial effect on outcomes than treatment without rtPA in Thai elderly patients is unknown. The purpose of this study was to compare stroke outcomes in patients aged over 70 years treated with and without intravenous thrombolysis.

### Materials and Methods

This was a case-control study. The number of patients on each arm was calculated by the following formula (equal to 82):

$$\frac{(Z_{1-\alpha}\sqrt{2P(1-P)} + Z_{1-\beta}\sqrt{P_1(1-P_1) + P_0(1-P_0)})^2}{(P_1 - P_0)^2}$$

where:

P1=0.40, P0=0.20, power of the test 80%, confidence level 95%.

One-hundred and five patients aged over 70 years with acute ischemic stroke treated with intravenous rtPA at Thammasat University Hospital, Thailand, between June 2007 and January 2011 were identified from the Thammasat Stroke Registry and were included in the study. One-hundred and five patients aged over 70 years who were seen from May 2010 to January 2011, and who were not treat-

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ed with intravenous thrombolysis, were included as control.

Intravenous rtPA was prescribed for acute ischemic stroke patients within 3 h of onset if there were no contraindications. However, after the publication of the European Cooperative Acute Stroke Study III (ECASS III), and the recommendations with regard to widening the time window for the treatment of acute ischemic stroke with intravenous rtPA issued by the American Heart Association/American Stroke Association,<sup>14,15</sup> we extended the time window for treatment with rtPA to 4.5 h. Most contraindications were the same as in the guidelines for treatment of acute ischemic stroke from the American Heart Association/American Stroke Association.<sup>14</sup> However, older age (>80 years old) was not an exclusion criterion. Patients with high blood pressure (systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg) were not excluded as long as blood pressure could be controlled by intravenous nicardipine (as defined by achieving target systolic blood pressure <185 mmHg and diastolic blood pressure <110 mmHg) before administration of rtPA. Abnormal findings from brain computed tomography (CT) including: i) hyperdense lesions suggestive of bleeding; and ii) hypodense lesions accounting for more than one-third of the middle cerebral artery (MCA) distribution were also contraindications for thrombolysis. Patients who were treated with

intravenous rtPA (0.9 mg/kg) were admitted to an intensive care unit or stroke unit to monitor and control blood pressure with a clinical follow up for the first 24 h. The severity of the stroke was evaluated using the National Institutes of Health Stroke Scale (NIHSS) by the same doctors before and after receiving rtPA. Another CT brain scan was performed within 36 h in all patients who received rtPA. However, follow-up brain CT was not routinely performed in all of those patients who were not treated with intravenous thrombolysis. The modified Rankin scale (mRS) was used to assess outcomes of the patients three months after the stroke onset. Symptomatic ICH was also classified by the National Institute of Neurological Disorders (NINDS) stroke rtPA criterion, *i.e.* hemorrhage associated with worsening of 1 point or more in the NIHSS score.<sup>16</sup> Early improvement was defined as having complete recovery or marked clinical improvement (decrease in NIHSS from baseline >8 points) 24 h after admission.

The base-line characteristics of patients, including age, gender, cardiovascular risk factors, blood glucose at presentation, platelet count, prothrombin time, severity of stroke, and stroke subtypes were studied. The measured outcome variables of this study were early improvement at 24 h, symptomatic intracerebral hemorrhage, favorable outcome (mRS 0-1) and death at three months. Patients' demographics, vascular risk factors and measured outcome variables were compared between those who were treated with and those without intravenous thrombolysis; an independent-samples t-test for continuous variables and the  $\chi^2$  test for dichotomous variables were used. The data are presented as means for continuous variables and percentage (number) for dichotomous variables. This study was approved by the human ethics committee of the Faculty of Medicine, Thammasat University, Thailand.

## Results

One-hundred and five patients aged over 70 years were not treated with intravenous rtPA during the study period; of these, 49 patients presented within 4.5 h after stroke onset. The reasons for not prescribing rtPA were: delays in the intervention process, *i.e.* late presentation, delay in laboratory or CT process ( $n=14$ , 28.6%); excessively mild stroke severity, *i.e.* NIHSS under 4 ( $n=12$ , 24.5%); rapid improvement ( $n=5$ , 10.2%); abnormal CT findings *i.e.* hypodense lesion over one-third of the MCA distribution ( $n=16$ , 32.7%); recent major surgery ( $n=1$ , 2%); and history of intracerebral hemorrhage, ICH ( $n=1$ , 2%). Follow-up CT or magnetic resonance imaging (MRI) was per-

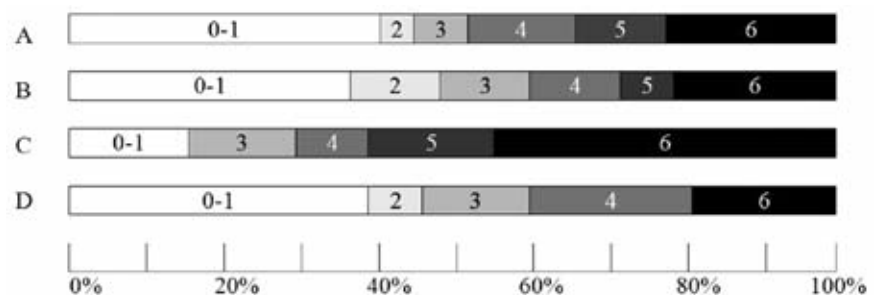
formed in 48 patients who did not receive rtPA. The base-line characteristics of the patients with and those without rtPA treatment are presented in Table 1. There were significant differences in base-line characteristics associated with older age (78 *vs* 76;  $P=0.03$ ), milder stroke (10 *vs* 13;  $P=0.001$ ), lower blood sugar at presentation (116 *vs* 135;  $P=0.026$ ) and reduced frequency of cardioembolic stroke (25% *vs* 42%;  $P=0.009$ ) in patients without the rtPA treatment as compared with those with the rtPA treatment. However, there was no significant difference in the rates of favorable outcomes (41% *vs* 37%;  $P=0.56$ ) or mortality (25% *vs* 22%;  $P=0.69$ ) in association with a marginally higher rate of symptomatic intracerebral hemorrhage (4% *vs* 14%;  $P=0.09$ ) in those receiving rtPA treatment. A significantly higher rate of early improvement at 24 h was found in patients treated with rtPA (4% *vs* 23%;  $P=0.001$ ). Univariate analysis and multiple logistical regression analysis were carried out to look for the factors associated with early improvement. Only rtPA treatment was related to early improvement (OR 14.1, 95% CI: 1.6-124.7) after adjustment for gender, stroke subtypes, hyperlipidemia, coronary artery disease, atrial fibrillation, antithrombotic treatment and symptomatic intracerebral hemorrhage. Stroke outcomes at three months as measured by the modified Rankin Scale (mRS) are presented in Figure 1.

There were significant differences in some base-line characteristics in the subgroup of patients aged over 80 years, with a greater history of hypertension and higher mean age, milder stroke, and a reduced risk of cardioembolic stroke in patients not receiving rtPA treatment (Table 1). Patients (>80 years old) treated with intravenous rtPA had a higher rate of favorable outcomes (40% *vs* 16%;  $P=0.137$ ) and a lower rate of mortality (22% *vs* 44%;  $P=0.128$ ) than patients not receiving rtPA treatment.

## Discussion

The number of elderly patients is increasing in most countries and consequently strokes in the very old (>80 years) subgroup occur more often; approximately one-third of all stroke patients are in this subgroup.<sup>17,18</sup> Mortality rates and non-dependency were higher in patients aged over 80 years as compared with the younger patients. Higher 1-month mortality rates were 31-34.6% in the very old patients (>80 years) as compared with the younger patients (13.4-16.7%); one study reported a 1-year mortality rate of 51.6%.<sup>19,20</sup> Disability after stroke (mRS  $\geq 3$ ) was reported in 78% of the very old patients who survived.<sup>20</sup> Our study showed that the 3-month mortality rate was 44% in patients aged over 80 years who did not receive rtPA treatment. Causes of high mortality may result from the reduced utilization of health care resources or the comorbidity and high proportion of atrial fibrillation reported in association with stroke.<sup>18,19,21</sup> Comorbidity, cognitive impairment, marital status, absence of caregivers and a lack of motivation that reduced the effectiveness of rehabilitation programs were potential contributors to the high level of disability observed in stroke survivors.<sup>22-25</sup>

Thrombolytic treatment in very old patients with acute ischemic stroke is still a subject of debate. The National Institute of Neurological Disorders and Stroke (NINDS) included all age ranges of the patients whereas the European Cooperative Acute Stroke Study (ECASS) excluded patients aged over 80 years.<sup>14,16</sup> Thus, the European Medicine Evaluation Agency has not approved thrombolysis with alteplase for use in patients aged over 80 years.<sup>26</sup> A systematic review and meta-analysis included 13 studies comparing outcomes after intravenous thrombolysis among 764 elderly patients (age  $\geq 80$  years) and 2792 patients under 80 years of



**Figure 1.** Stroke outcome at 3 months in patients treated with and without intravenous thrombolysis, classified by modified Rankin Scale (mRS). (A) Patients aged over 70 years without intravenous thrombolytic treatment. (B) Patients aged over 70 years with thrombolytic treatment. (C) Patients aged over 80 years without intravenous thrombolytic treatment. (D) Patients aged over 80 years with thrombolytic treatment.

age. Elderly patients achieved less favorable outcomes (OR 0.49, 95% CI: 0.40-0.61) and showed higher mortality rates (OR 2.77, 95% CI: 2.25-3.40) but not significantly higher symptomatic ICH rates (OR 1.31, 95% CI: 0.93-1.84) as compared with patients under 80 years old.<sup>27</sup> Ford *et al.* studied outcomes and symptomatic ICH rates in 19,411 patients aged 80 years or under and 1831 patients aged over 80 years in the Safe Implementation of Treatment in Stroke - International Stroke Thrombolysis Register (SITS-ISTR).<sup>3</sup> Here patients over 80 years of age had a higher mortality rate (30% *vs* 12%, OR 1.53, 95% CI: 1.43-1.65) and were less independent (35% *vs* 57%, OR 0.73, 95% CI: 0.68-0.78). There was a non-significant increase in the symptomatic ICH rate according to NINDS criteria in the older

subgroup (9.5% *vs* 7.8%, OR 0.96, 95% CI: 0.87-1.06). Mishra *et al.* assessed the effect of age in response to alteplase by comparing 23,334 patients who received thrombolysis from the SITS-ISTR (during 2002-2009) with a control group made up of 6166 patients who participated in VISTA neuroprotection trials (during 1998-2007) and were not treated with rtPA.<sup>28</sup> Among the subgroup of patients aged over 80 years, 2235 and 1237 patients were treated with and without rtPA, respectively. As compared with a control subgroup, very old patients (>80 years) treated with rtPA had a higher rate of favorable outcomes (mRS 0-2) (OR 2.1, 95% CI: 1.7-2.5) and a marginally lower mortality rate (OR 0.89, 95% CI: 0.76-1.0). The third international stroke trial (IST-3) compared the efficacy and safety of rtPA *vs*

placebo, with a sample size of 3035 patients and including 1617 patients aged over 80 years.<sup>7</sup> In a subgroup of patients aged over 80 years, the rate of favorable outcome was higher in those receiving rtPA treatment (27.3% *vs* 23.5%, OR 1.35, 95% CI: 0.97-1.88) and this did not differ significantly from the younger patients. Our study showed non-significant differences in the rates of favorable outcomes, symptomatic intracerebral hemorrhages and mortality in patients aged over 70 years with or without thrombolytic treatment. However, there were significant differences in several base-line characteristics between the groups. Older age, severe stroke, high blood glucose, cardioembolic stroke had been reported to be the independent factors of poor outcomes and death. Thus, it is not possible to conclude that

**Table 1. Base-line characteristics and outcomes in aging patients (>70 years old) treated with and without intravenous recombinant-tissue plasminogen activator.**

Baseline characteristics	>70 years old		P	>80 years old		P
	No rtPA (N=105)	rtPA (N=105)		No rtPA (N=32)	rtPA (N=18)	
Mean age (years) (median, range)	78±6 (76, 71-94)	76±5 (75, 71-92)	0.033	87±4	85±4	0.325
Mean NIHSS	10±7	13±7	0.001	11±7	15±9	0.188
Mean NIHSS at 24 h	10±8	10±8	0.784	11±7	11±9	0.926
Mean prothrombin time (seconds)	13.4±10.3	12.2±2.1	0.263	15.7±14	12.7±1.5	0.391
Mean INR	1.05±0.15	1.04±0.16	0.919	1.03±0.95	1.09±0.2	0.317
Mean platelet count (×10 <sup>9</sup> /L)	228±74	238±81	0.419	222±59	230±59	0.662
Mean LDL (mg/dL)	122±44	116±36	0.270	121±34	117±37	0.703
Mean blood glucose at presentation (mg/dL)	116±49	135±70	0.026	116±43	136±74	0.322
Gender						
Male	57 (54%)	55 (52%)		11 (34%)	8 (44%)	
Female	48 (46%)	50 (48%)	0.782	21 (66%)	10 (56%)	0.481
NIHSS at presentation						
0-5	39 (37%)	14 (13%)		7 (22%)	2 (11%)	
6-10	24 (23%)	30 (29%)		10 (31%)	5 (28%)	
11-15	17 (16%)	18 (17%)		6 (19%)	2 (11%)	
>15	25 (24%)	43 (41%)	0.001	9 (28%)	9 (50%)	0.434
Hypertension	71 (68%)	74 (71%)	0.654	23 (72%)	7 (39%)	0.022
Diabetes mellitus	24 (23%)	19 (18%)	0.939	8 (25%)	3 (17%)	0.724
Hyperlipidemia	30 (29%)	30 (29%)	1.000	7 (22%)	3 (17%)	0.730
Coronary artery disease	14 (13%)	16 (15%)	0.693	4 (13%)	3 (17%)	0.692
Old ischemic stroke	4 (4%)	10 (10%)	0.093	1 (3%)	2 (11%)	0.291
Transient ischemic attack	2 (2%)	4 (4%)	0.683	1 (3%)	-	-
Atrial fibrillation	29 (28%)	36 (34%)	0.296	12 (38%)	5 (28%)	0.486
Smoking	15 (14%)	20 (19%)	0.355	4 (13%)	5 (28%)	0.253
Antithrombotic use	36 (34%)	37 (35%)	0.847	10 (32%)	3 (17%)	0.315
Stroke subtype						
LAA	31 (30%)	33 (31%)		7 (22%)	7 (39%)	
SAO	37 (35%)	26 (25%)		13 (41%)	3 (17%)	
CE	26 (25%)	44 (42%)		9 (28%)	8 (44%)	
UND	11 (10%)	2 (2%)	0.009	3 (9%)	-	0.144
Early improvement at 24 h	4 (4%)	24 (23%)	0.001	-	4 (22%)	0.058
Asymptomatic intracerebral hemorrhage	11 (23%)	32 (31%)	0.318	2 (14%)	3 (17%)	1.000
Symptomatic intracerebral hemorrhage	2 (4%)	14 (14%)	0.095	1 (7%)	-	0.438
Favorable outcome at 3 months	43 (41%)	39 (37%)	0.557	5 (16%)	7 (40%)	0.137
Mortality rate at 3 months	26 (25%)	23 (22%)	0.690	14 (44%)	4 (22%)	0.128

rtPA, recombinant tissue-plasminogen activator; NIHSS, National Institutes of Health Stroke Scale.



thrombolytic treatment is ineffective in aging patients. Differences in favorable outcomes and death between those with and without rtPA treatment were obvious in subgroups of patients aged over 80 years. Patients with the rtPA treatment had a higher rate of favorable outcomes (40% vs 16%;  $P=0.137$ ) and a lower rate of mortality (22% vs 44%;  $P=0.128$ ) compared with those without the rtPA treatment. However, the difference did not reach statistical significance, which may largely be due to the small number of patients in this subgroup.

The mechanism of early recovery or improvement is not clearly understood. A transcranial Doppler (TCD) study in patients treated with rtPA found that the timing of arterial recanalization, as determined by TCD, correlated with early clinical recovery from stroke.<sup>29</sup> Several studies reported a similar proportion of successful recanalization in patients aged over 80 years to that achieved in younger patients.<sup>3</sup> Our study showed that early improvement within 24 h after stroke onset was found more frequently in patients who received the rtPA treatment, which may represent a higher rate of recanalization.

## Conclusions

Our study has some limitations. Firstly, this was a retrospective review of sequential cases and was not a randomized controlled study. Non-thrombolytic patients (>70 years of age) were classified by the duration of time required to reach similar numbers to those achieved in patients treated with rtPA. Significant differences in base-line characteristics of the two groups were noted. The differences in stroke severity between the case and control groups may represent more rapid stroke awareness in patients with more severe stroke, as this subgroup of patients was more likely to receive thrombolytic treatment. However, for the subgroup of the patients aged over 80 years, characteristics were fairly similar. Second, a follow-up brain CT or MRI was not performed in some of the patients who did not receive rtPA treatment; therefore, the rate of asymptomatic intracerebral hemorrhage may be underestimated.

This is the first study in Thailand comparing stroke outcomes in aging patients with and without rtPA treatment. The study showed that the very old patients receiving rtPA did not have poorer outcomes. Further randomized controlled studies are still needed to confirm the suggested benefit of thrombolysis in aging Asian patients.

In conclusion, in subgroups of patients aged over 80 years, this retrospective review revealed that there was a trend of higher rate of favorable outcome and lower mortality in patients receiving rtPA treatment.

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