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Brief communication (Original)

Risk factors for intracerebral hemorrhage after treatment with recombinant tissue-type plasminogen activator for acute ischemic stroke

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Background: Acute stroke is a common neurological disorder. Intravenous recombinant tissue-type plasminogen activator (rt-PA) treatment is recommended for treatment of patients with acute ischemic stroke. A major side effect of rt-PA is intracerebral hemorrhage (ICH). Studies of the risks for ICH after rt-PA treatment in Asian populations are limited.

Objective: To determine risk factors for intracerebral hemorrhage after treatment of acute ischemic stroke with rt-PA and create online tool to calculate the risk.

Methods: We reviewed all patients with acute ischemic stroke who received treatment with rt-PA within 4.5 hours of stroke onset at the stroke fast track unit, Srinagarind Hospital, Khon Kaen University, Thailand. The study period was between November 2008 and September 2011. Factors associated with ICH after rt-PA treatment were analyzed by multivariate logistic regression.

Results: There were 162 patients with acute ischemic stroke who received rt-PA treatment within 4.5 hours. Of those, 12 patients (7.41%) developed ICH. Only baseline modified Rankin scale score was significantly associated with ICH. The adjusted odds ratio was 1.733 (95% CI 1.008 to 2.982). An online tool to calculate the risk is available at http://202.28.94.20/research/.

Conclusions: Intracerebral hemorrhage after rt-PA treatment of patients with acute stroke was low at 7.41% and related to baseline functional status.

Keywords: Acute stroke, complication, intracerebral hemorrhage, ischemic, modified Rankin scale, recombinant tissue-type plasminogen activator, rt-PA, thrombolytic

Acute stroke is the most common neurological disorder worldwide. Its incidence is approximately 9 million people per year (WHO) with a mortality of 64.21 persons/100,000 population [1]. The incidence is increasing. Stroke may cause neurological sequelae and disability. It is ranked as 6th for disease causing morbidity.

Intravenous recombinant tissue-type plasminogen activator (rt-PA) treatment is recommended for patients with acute ischemic stroke. The newly described "golden period" for rt-PA treatment is 4.5 hours after stroke occurrence [2]. Compared with placebo, rt-PA treatment improves clinical outcome. However, symptomatic intracerebral hemorrhage occurs more frequently in the rt-PA group (2.4% vs 0.2%; P = 0.008). Risk factors for intracerebral hemorrhage after rt-PA treatment have been explored. Functional status and infarct size may increase the risk of intracerebral hemorrhage after rt-PA treatment [2]. However, in the Thai population these data are limited, particularly after the new "golden period" era.

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Methods

The study protocol was approved by the Khon Kaen University Ethics Committee for Human Research (approval No. HE541372).

We reviewed the cases of all patients with acute ischemic stroke who received treatment with rt-PA within 4.5 hours of stroke onset at the stroke fast track unit, Srinagarind Hospital, Khon Kaen University, Thailand. The study period was November 2008 and September 2011. This study used the same dataset as that in a previously published article [3].

All baseline clinical features were recorded including age, sex, baseline National Institutes of Health Stroke Scale (NIHSS) [4], baseline modified Rankin scale (mRS) [5], time from the onset of symptoms to computed tomography (CT) of the brain in minutes, time from the onset to rt-PA treatment, Alberta Stroke Program Early CT score (ASPECTS) [3], and characteristics of CT brain findings.

Patients were divided into two groups; with or without intracerebral hemorrhage as seen by the summary discharge sheet. Baseline and clinical characteristics of patients between both groups were compared using descriptive statistics. Univariate logistic regression analyses were applied to calculate the crude odds ratios (OR) of individual variables for having intracerebral hemorrhage. All clinically significant variables or $P < 0.20$ by univariate analyses were included in subsequent multivariate logistic regression analyses. Analytical results were presented as crude OR, adjusted OR, and 95% confidence intervals (CI). Data analyses were performed with STATA software (College Station, TX, USA).

An online tool to predict the risk for intracerebral hemorrhage after rt-PA treatment was produced by using the final model of multivariate logistic regression analysis. The probability equals $1/[1+e^{-x}]$. X refers to the constant value and coefficient value of all factors in the final model.

Results

There were 162 patients with acute ischemic stroke who received rt-PA treatment within 4.5 hours. Of those, 12 patients (7.41%) developed intracerebral hemorrhage. Patients with intracerebral hemorrhage had comparable clinical features to those who did not have intracerebral hemorrhage (**Table 1**). However, the baseline NIHHS, and the baseline mRS were higher in those who had intracerebral hemorrhage (NIHHS: 13 vs 9.5; mRS: 4 vs 3) than those who did not have intracerebral hemorrhage. By multivariate logistic regression analysis, only baseline mRS was significantly associated with having intracerebral hemorrhage. The adjusted odds ratio was 1.733 (95% CI 1.008 to 2.982).

Table 1. Clinical factors between patients with acute stroke who received rt-PA treatment within 4.5 hours categorized by the occurrence of intracerebral hemorrhage (ICH)

Variables	No hemorrhage (n = 150)	ICH (n = 12)	*P*
Age, years	65 (55–74)	71 (55.50–75)	0.616
Male sex, n	80 (53.33)	4 (33.33)	0.235
Baseline NIHHS	9.5 (6–13)	13 (7.5–16)	0.092
Baseline mRS	3 (2–4)	4 (3–4.5)	0.081
Time to CT, min	86.5 (64–116)	99 (76–162)	0.390
Time to rt-PA, min	128.5 (103–161)	139 (116–202)	0.443
Received rt-PA 3-4.5 hour	25 (16.67)	4 (33.33)	0.230
ASPECTS score	7 (5–9)	7 (5–8.5)	0.628
Dense MCA	43 (28.67)	3 (25.00)	0.999
Caudate lesion	53 (35.33)	6 (50.00)	0.357
Left side lesion	57 (38.00)	5 (41.67)	0.999

Data presented as median (1st and 3rd quartile) or numbers (percentage), NIHHS = National Institutes of Health Stroke Scale, mRS = modified Rankin scale, CT = computed tomography, rt-PA = recombinant tissue-type plasminogen activator, ASPECTS = Alberta Stroke Program Early CT score, MCA = middle cerebral artery

An online tool is available at http://202.28.94.20/research/. The X value in the formula was calculated using the following equation; X = –4.07 + [0.56 × mRS] – [0.68 × dense middle cerebral artery; 0 if no, 1 if yes] – [0.005 × time to CT in minute] + [1.46 × rt-PA treatment period; 0 if less than 3 hours, and 1 for 3 to 4.5 hours].

Discussion

Use of streptokinase in treatment of acute ischemic stroke is prone to adverse reactions [6]. A randomized, placebo-controlled trial of streptokinase was stopped early because of an increased risk of intracerebral hemorrhage. The mortality and disability outcome between streptokinase and the placebo groups was not different at six months. However, patients in the streptokinase group had significantly higher mortality at 10 days after treatment (34.0% vs 18.2%). Intracerebral hemorrhage was 21.2% vs 2.6% in the placebo group. At present, rt-PA is considered an effective and safer thrombolytic agent for acute ischemic stroke treatment than streptokinase [2]. Nevertheless, intracerebral hemorrhage remains an important side effect, even with rt-PA.

The rate of intracerebral hemorrhage after rt-PA treatment is 7.41%, which was somewhat higher than previous reports [2, 7]. A report from central Thailand found the rate was 5.7% in 192 patients who received rt-PA treatment in the new window period as used in this study [8].

There are several risk scores to predict risk of intracerebral hemorrhage, such as the HAT score [9], the DRAGON score [10], or the SEDAN score [11]. The DRAGON and SEDAN scores suggested that a dense middle cerebral artery sign is a predictor for intracerebral hemorrhage after rt-PA treatment, but not in this study. The HAT and SEDAN score had NIHHS score as a significant predictor. The present study showed that mRS score is the only predictor for intracerebral hemorrhage after rt-PA treatment. The mRS may be similar to NIHHS score in terms of functional status evaluation before rt-PA treatment. These mentioned scores are derived from studies conducted in the Western countries. The HAT score is valid for predicting the risk of intracerebral hemorrhage after rt-PA treatment in Taiwanese patients [12]. A study from Thailand found that atrial fibrillation, and NIHHS were associated with (asymptomatic) post rt-PA treatment intracerebral hemorrhage. It seems that baseline functional status may be a clinical predictor for post rt-PA treatment intracerebral hemorrhage; either NIHHS ≥15 or high mRS score. An increase in mRS score at baseline of 1 will increase the risk of intracerebral hemorrhage by 1.75 times (**Table 2**). An online tool is provided by the final model of multivariate logistic regression by this study.

Baseline NIHHS score is used as a contraindication for rt-PA treatment. A baseline NIHHS score more than 25 is not eligible for rt-PA treatment [2]. In addition, baseline NIHHS and ASPECTS scores are factors associated with long term functional outcomes in patients who have suffered from an acute stroke. However, neither factor is associated with the risk for intracerebral hemorrhage after rt-PA treatment in this study by either univariate or multivariate logistic regression analyses. Only mRS score was significantly associated with intracerebral hemorrhage. The mRS score is more practical to determine than NIHHS and ASPECTS scores in clinical practice [3].

In conclusion, baseline functional status may associate with intracerebral hemorrhage after rt-PA treatment in acute stroke patients.

Table 2. Factors associated with intracerebral hemorrhage after rt-PA treatment in acute stroke patients

Variables	Univariate odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Baseline mRS score	1.535 (0.927 to 2.542)	1.746 (1.008 to 3.023)
Dense middle cerebral artery	0.829 (0.214 to 3.211)	0.505 (0.118 to 2.153)
Time to computed tomography	1.005 (0.994 to 1.018)	0.995 (0.975 to 1.016)
Received rt-PA within 3–4.5 hours	2.500 (0.699 to 8.944)	4.304 (0.407 to 45.530)

mRS = modified Rankin scale, rt-PA = recombinant tissue-type plasminogen activator, CI = confidence interval

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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