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Leukoaraiosis and stroke severity scores in post-rtPA intracerebral haemorrhage

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ABSTRACT

Introduction Post thrombolytic symptomatic intracerebral haemorrhage (sICH) is a major concern in patients who had acute ischaemic stroke. Leukoaraiosis (LA) is reported to be related with sICH after intravenous thrombolytic treatment. However, the influence of LA and stroke neurological and imaging severity scores is still debated.

Objective To evaluate if LA or severity scores are related with sICH in patients who had acute ischaemic stroke who received thrombolytic therapy. And, predictors for sICH were also studied with adjustment of baseline severity scores.

Methods This was a retrospective, analytical study. The inclusion criteria were adult patients diagnosed as acute ischaemic stroke who received the recombinant tissue plasminogen activator (rtPA) treatment within 4.5 hours. The study period was between May 2007 and November 2016. Predictors for sICH were determined using logistic regression analysis.

Results During the study period, there were 504 eligible patients. Of those, 45 patients (8.92%) had sICH. Among nine factors in the final model for predicting sICH, there were four independent factors including previous antiplatelet therapy, previous anticoagulant therapy, presence of LA and hyperdense artery sign. The highest adjusted OR was previous anticoagulant therapy (5.08 with 95% CI of 1.18 to 11.83), while the LA factor had adjusted OR (95% CI) of 2.52 (1.01 to 6.30).

Conclusions LA, hyperdense artery sign, previous antiplatelet therapy and previous anticoagulant therapy were associated with post-rtPA sICH. Further studies are required to confirm the results of this study.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Leukoaraiosis (LA) is reported to be related with symptomatic intracerebral haemorrhage after intravenous thrombolytic treatment. However, the influence of LA and stroke neurological and imaging severity scores is still debated.

WHAT THIS STUDY ADDS

⇒ LA, hyperdense artery sign, previous antiplatelet therapy and previous anticoagulant therapy were associated with post intravenous thrombolytic treatment symptomatic intracerebral haemorrhage.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Clinicians should be aware of post intravenous thrombolytic treatment symptomatic intracerebral haemorrhage in patients with LA and other predictive signs from baseline CT of the brain.

INTRODUCTION

The American Heart Association reported that the prevalence of stroke was 42.4 million people: 57.11% were ischaemic stroke and associated with several diseases.[1–5] Stroke mortality was ranked as the second-leading cause of death with 6.3 million people or 11.8% of total death worldwide. Intravenous recombinant tissue plasminogen activator (rtPA) is effective in an acute ischaemic stroke with a golden period of 4.5 hour of stroke onset.[6] However, symptomatic intracerebral haemorrhage (sICH) may cause significant morbidity and mortality.[7] The sICH was reported to be as high as 15.7% with several risk factors including age (OR of 1.03/year), National Institutes of Health Stroke Scale (NIHSS) of 1.08/point or leukoaraiosis or LA (2.45).

LA, a small vessel disease, is a condition with vascular damage and blood-brain barrier dysfunction causing white matter lesions. A meta-analysis found that it is related with sICH after intravenous thrombolytic treatment.[8] The ORs (95% CI) was 1.30 (1.19 to 1.42). However, the included studies had conflicting outcomes particularly with severity scores such as NIHSS or the Alberta Stroke Program Early CT Score (ASPECT Score). Therefore, this study aimed to evaluate if LA or severity scores are related to sICH in patients who had acute ischaemic stroke who received thrombolytic therapy. And, predictors for sICH were also studied with adjustment of baseline severity scores.

METHODS

This was a retrospective, analytical study conducted at Srinagarind Hospital, a University Hospital, Khon Kaen University, Thailand. The inclusion criteria were adult patients diagnosed as acute ischaemic stroke

who received the rtPA treatment within 4.5 hours. The study period was between May 2007 and November 2016.

The eligible patients were evaluated for baseline characteristics, stroke types and imaging of the brain. Baseline characteristics included age, sex, comorbid diseases, previous antiplatelet/anticoagulant therapy and the NIHSS. The stroke types were defined as large-artery atherosclerosis, cardioembolism and small-vessel occlusion. For imaging findings, the ASPECT Score, presence of LA (grade I–IV)[9] and hyperdense artery sign. The cut-off point for NIHSS score was 6 or more indicating moderate stroke,[10] while ASPECT of less than 6 indicated brain oedema which may increase the risk of bleeding.[11 12] These two cut-off points were used for the analysis. Note that anticoagulant therapy in this study was warfarin and those who received warfarin prior to the intravenous thrombolytic therapy had an international normalised ratio (INR) of less than 1.7.

The LA grading was scored with 0–2 in two regions: anterior horns of the lateral ventricles and white matter around the posterior part of the cella media and the posterior part of the centrum semiovale. The details for scoring were none (0); abnormality was restricted to the region adjoining the ventricles (1) and the increased hypodensity involved the entire region from lateral ventricle to the cortex (2). If there were differences between sides of the brain, the highest score was used. The total score was a summation of both regions; ranging from 0 to 4.[9] These scores were defined by one radiologist (AB) and one neurologist (KK) independently. A disconcordant of the score was solved by a discussion of both scorers. The outcome of this study was sICH.

Details of imaging analysis were as follows: a non-contrast multi-slice CT brain (Somatom plus 4, Siemens) scan was routinely performed in all patients who had acute ischaemic stroke with the standard brain protocol, continuous 6-mm slice thickness through the posterior fossa and an 8-mm slice thickness through the supraclinoidal brain. Post-treatment non-contrast CT scans are performed in a similar fashion and within 24 hours after rtPA treatment. All CT scans were reanalysed by two observers blinded to clinical details apart from the side of neurologic deficits and primary radiologic diagnosis. The sICH or haemorrhagic transformation was made by the European Cooperative Acute Stroke Study (ECASS) criteria[13] by evidence of blood at any site in the brain on the CT scan, documentation by the investigator of clinical deterioration, or adverse events indicating clinical worsening (eg, drowsiness, increase of hemiparesis) or causing a decrease in the NIHSS score of 4 or more points in the first 72 hours after thrombolytic treatment.

Statistical analyses

Eligible patients were classified into either with or without sICH. Descriptive statistics were used to compare the differences between the two groups. Predictors for sICH were determined using logistic regression analysis. The unadjusted ORs and p values of the studied variables were evaluated using univariate logistic regression analysis. Potentially significant factors with a p value of less than 0.20 according to univariate logistic regression analysis or those with clinically significant were subjected to subsequent multivariate logistic regression analysis. An area of a receiver operating characteristic (ROC) curve was reported for the predictive model to show discrimination ability of the model. The best predictive model was the one with the highest area under the ROC curve. The analyses were performed using STATA (College Station, Texas, USA).

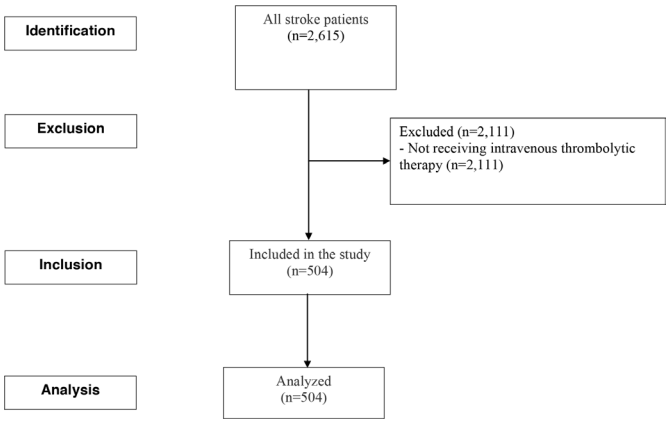

Figure 1 A STROBE flow chart for patient selection. STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

RESULTS

During the study period, there were 2615 diagnosed as acute stroke. Of those, 2111 patients were excluded due to no intravenous thrombolytic therapy. In total, 504 patients were included in the study (figure 1). Of those, 45 patients (8.92%) had sICH. Between both groups, there were seven significant factors (table 1). The sICH group had older age (70.2 vs 64.3 years), higher mean NIHSS Score (15.0 vs 10.8), higher proportion of large-artery atherosclerosis (48.9% vs 29.4%), higher LA grade III–IV (17.8% vs 7.2%), higher ASPECT Score <6 (51.1% vs 19.8%) and higher hyperdense artery sign (57.8% vs 24.8%) than the non-sICH group. The sICH group also had lower proportion of small-vessel occlusion (11.1% vs 38.8%) than the non-sICH group.

Among nine factors in the final model for predicting sICH, there were four independent factors including previous antiplatelet therapy, previous anticoagulant therapy, presence of LA and hyperdense artery sign (table 2). These factors were positively related with sICH. The highest adjusted OR was previous anticoagulant therapy (5.08 with 95% CI of 1.18 to 11.83), while the LA factor had adjusted OR (95% CI) of 2.52 (1.01 to 6.30). The final model had predictive ability for sICH with the area under the ROC curve of 0.77 (95% CI 0.71 to 0.85).

Table 1 Baseline characteristics and imaging findings of patients who had acute ischaemic stroke with leukoaraiosis (LA) categorised by presence of symptomatic intracerebral haemorrhage (sICH) after intravenous thrombolytic therapy

Factors	No sICH, n=459	sICH, n=45	P value
Mean (SD) age, years	64.3 (13.3)	70.2 (9.6)	0.002
Male sex	257 (56.0)	20 (44.4)	0.137
Comorbid diseases			
Hypertension	234 (51.0)	26 (57.8)	0.380
Dyslipidaemia	115 (25.1)	7 (15.6)	0.158
Diabetes mellitus	127 (27.7)	18 (40)	0.080
Atrial fibrillation and flutter	122 (26.6)	18 (40)	0.050
Myocardial infarction	32 (7)	3 (6.7)	0.999
Previous antiplatelet therapy	120 (26.1)	21 (46.7)	0.003
Previous anticoagulant therapy	12 (2.61)	3 (6.67)	0.140
Mean systolic blood pressure (SD), mm Hg	149.6 (28.7)	156.0 (26.1)	0.103
Mean diastolic blood pressure (SD), mm Hg	84.9 (16.2)	85.9 (15.6)	0.515
Median (range) NIHSS	9 (1–39)	16 (4–27)	<0.001
Types of stroke			
Large-artery atherosclerosis	135 (29.4)	22 (48.9)	0.007
Cardioembolism	145 (31.6)	18 (40)	0.248
Small-vessel occlusion	178 (38.8)	5 (11.1)	<0.001
Imaging			
LA findings			0.001
No LA	188 (41.0)	8 (17.8)	
LA grade I–II	238 (51.8)	29 (64.4)	
LA grade III–IV	33 (7.2)	8 (17.8)	
ASPECT Score			<0.001
7–10	368 (80.2)	22 (48.9)	
4–6	64 (13.9)	16 (35.5)	
<4	27 (5.9)	17 (15.6)	
Hyperdense artery sign	114 (24.8)	26 (57.8)	<0.001

Data presented as number (%) unless indicated otherwise.
ASPECT Score, The Alberta Stroke Programme Early CT Score; NIHSS, National Institutes of Health Stroke Scale.

DISCUSSION

This study found that the sICH post thrombolytic therapy was comparable with the previous study: 8.92% in this study and 8.8% in the ECASS II trial.[13] For LA, it was an independent factor for sICH as previously reported.[14] The adjusted OR of LA in this study was slightly lower than the previous report (2.52 vs 2.9). However, some studies found that LA was not an independent factor for sICH after thrombolytic therapy including a study from Korea.[15–17] This study may be the first study in Asian population to show that LA was associated with sICH in post-rtPA treatment. There are several proposed mechanisms such as decreased connectivity and plasticity of brain or damage of endothelium.[15 18]

Previous studies found that NIHSS and ASPECT Scores were significantly related to sICH post thrombolytic therapy.[7 15 19] In this study, both scores were not a significant factor after adjusted (table 2). Another significant factor was hyperdense artery sign which is an indicator for large infarction area as previously reported.[19] Combination with the LA result, it may indicate that large vessel lesion or poor small vessel lesion or LA were two dominating factors over the severity assessment scores both ASPECT and NIHSS.

The other interesting findings in this study are previous antiplatelet and anticoagulant therapy. These two factors were also independently associated with the sICH even after adjusted for age, sex, LA, large vessel lesion or severity scores. A previous meta-analysis also found that antiplatelet may increase the risk of sICH but not anticoagulant.[7] The same study also found that prolong prothrombin time was an independent factor for post-rtPA sICH though: OR of 1.24 (95% CI 1.04 to 1.46). These findings may raise concern on primary prevention by both agents and also patient selection for rtPA treatment. Note that those patients received

Table 2 Factors associated with symptomatic intracerebral haemorrhage (sICH) after intravenous thrombolytic therapy in patients who had acute ischaemic stroke with leukoaraiosis (LA)

Factors	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age	1.04 (1.01 to 1.07)	1.01 (0.97 to 1.04)
Male sex	0.63 (0.34 to 1.16)	0.73 (0.37 to 1.44)
Atrial fibrillation and flutter	1.84 (0.98 to 3.42)	0.83 (0.40 to 1.71)
Previous antiplatelet	2.47 (1.33 to 4.60)	2.35 (1.20 to 4.61)
Previous anticoagulant	2.66 (0.72 to 9.80)	5.08 (1.18 to 11.83)
NIHSS >6	1.10 (1.05 to 1.15)	3.56 (0.79 to 5.88)
LA	5.70 (2.00 to 6.24)	2.52 (1.01 to 6.30)
ASPECT Score <6	4.18 (2.08 to 8.39)	1.37 (0.50 to 3.75)
Hyperdense artery sign	4.14 (2.21 to 7.76)	3.79 (1.85 to 7.73)

ASPECT Score, The Alberta Stroke Programme Early CT Score; NIHSS, National Institutes of Health Stroke Scale.

warfarin treatment prior to the intravenous thrombolytic therapy were mostly due to atrial fibrillation, only two patients did not have AF. These patients had the INR less than 1.7 prior to the intravenous thrombolytic therapy. These findings may indicate that baseline INR before the intravenous thrombolytic therapy may need to be lower than 1.5 or not. However, this suggestion may need further studies as there were few patients with anticoagulant therapy in this study.

There are some limitations in this study. First, this study was conducted in a university hospital. Therefore, the results of this study may not be applicable for other settings such as community hospitals. Second, the results may imply that LA is also a risk for post-rtPA sICH in Asian populations. However, further studies are required. Finally, some related conditions such as sleep apnoea were not evaluated in individuals.[20–25]

CONCLUSIONS

LA, hyperdense artery sign, previous antiplatelet therapy and previous anticoagulant therapy were associated with post-rtPA sICH. Further studies are required to confirm the results of this study.

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Competing interests None declared.

Patient consent for publication Not applicable.

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