Relationship between Atrial Fibrillation and Worse Outcomes in Stroke Patients after Intravenous Thrombolysis

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Abstract

Background: Atrial fibrillation (AF) is considered a predictor for severe stroke and poor outcome. However, It is unclear whether AF is associated with poor outcome in acute ischemic stroke patients treated with intravenous thrombolysis. To investigate the effect of AF on stroke outcomes among rtPA-treated patients is essential for optimizing approach to patient management.

Objective: The aim was to evaluate whether AF is associated with poor outcome in acute ischemic stroke patients treated with intravenous thrombolysis and to investigate the relationship between pre-stroke CHA_2DS2-VASc scores and the difference in outcomes following IV thrombolysis among patients with AF.

Methods: We retrospectively identified acute ischemic stroke patients who received intravenous recombinant tissue plasminogen activator (IV rtPA) treatment at the Faculty of Medicine Vajira Hospital between June 2005 to June 2021 from our institutional stroke database. All eligible patients were divided into two groups by presence of AF. Vascular risk factors, stroke characteristics, and outcome measures were compared between patients with and without AF. Multiple logistic regression was performed to identify factors associated with unfavorable outcome (modified Rankin scale at 90 days >2) and symptomatic ICH.

Result: 141 patients were included in our analysis (mean age, 66.2 years, with 50% of patients being men) . There were 46 (32.62 %) patients had AF. 14 patients had a first-detected episode of AF, and 32 patients had chronic AF. The incidence of symptomatic intracerebral hemorrhage was significantly higher in patients with AF than in

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patients without AF (45.7% vs 11.6%), and the incidence of unfavorable functional outcome was significantly higher in patients with AF than in patients without AF (71.7% vs 32.6%).

The increase risk of symptomatic intracerebral hemorrhage among patients with AF remained significant after adjusting for age and baseline National Institutes of Health Stroke Scale score (odds ratio, 4.21 [95% CI, 1.69-10.51]). The increase risk of unfavorable functional outcome among patients with AF remained significant after adjusting for age and baseline National Institutes of Health Stroke Scale score (odds ratio, 3.08 [95% CI, 1.27 -7.48]). There were no differences in outcomes between patients with a first-detected episode of AF and patients with chronic AF. Patients with AF who had CHA_2DS_2-VASc Score>3 had a higher incidence of symptomatic ICH and unfavorable functional outcome compared with those who had CHA_2DS_2-VASc Score ≤3.

Conclusion: Patients with AF had significantly a higher incidence of symptomatic ICH and unfavorable functional outcome after intravenous thombolysis when compared to those without AF and patients with AF who had CHA_2DS_2-VASc Score>3 had a higher incidence of symptomatic ICH and unfavorable functional outcome compared with those who had CHA_2DS_2-VASc Score ≤3.

Keywords: Acute ischemic stroke, Recombinant tissue plasminogen activator, Thrombolysis, Atrial fibrillation

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in Thailand.[1] Acute ischemic stroke is increasing by age and presence of AF.[2] Acute ischemic stroke patients also had poor prognosis if AF is one of the comorbid disease.[3-8] A previous study found that acute ischemic stroke patients without AF had a 30-day mortality rate at 10.2%. This mortality rate was increased to 22.3% in patients with AF.[9] A study from Thailand also found similar findings; the mortality rate of acute ischemic stroke patients was higher in AF than non-AF group significantly (14.1% vs. 6.2%; p-value <0.001) including intracerebral hemorrhage from rtPA and duration of hospital duration.[10]

Currently, thrombolytic therapy by a recombinant tissue plasminogen activator (rtPA) is a standard treatment for acute ischemic stroke. Several stroke outcomes including functional status or mortality rate were significantly improved if rtPA was given within 4.5 hours[11,12] and early recanalization is considered as a powerful marker of this improvement.[13,14] However, AF was associated with a low rate of early recanalization after recombinant tissue plasminogen activator (rtPA) treatment[15], with a low rate of early major neurological improvement [16] and poor outcome after intravenous thrombolysis.[17] It is unclear whether patients with AF (whether it be a first-detected episode of AF or chronic AF) would respond differently to rtPA treatment and whether the burden of AF has any consequence on stroke outcomes.

The aim was to compare clinical characteristics and outcomes in acute ischemic stroke patients presenting with and without AF treated with intravenous thrombolysis and to assess whether the presence of AF could be a predictor of poor clinical outcome after intravenous thrombolysis.

Objective

1. To evaluate whether AF is associated with poor outcome in acute ischemic stroke patients treated with intravenous thrombolysis.

2. To investigate the relationship between pre-stroke CHA_2DS_2-VASc scores and the difference in outcomes following IV thrombolysis among patients with AF.

Methods

We retrospectively identified acute ischemic stroke patients who were treated with IV rtPA at the Faculty of Medicine Vajira Hospital between June 2005 to June 2021 from our institutional stroke database. All patients eligible for IV rtPA treatment were included. Eligibility criteria and contraindications for IV rtPA at our institute were the same as those set forth in the National Institute of Neurological Disorders and Stroke (NINDS) study.[18] Those with incomplete data and different final diagnosis other than acute ischemic stroke, and patients without follow-up data at three months were exclude.

All eligible patients were divided into two groups by presence of AF. Baseline characteristics and stroke outcomes of all patients were recorded. Collected baseline demographic and medical history included: age, sex, body weight, height, body mass index (BMI), history of hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, and atrial fibrillation. Laboratory data included: hemoglobin, white blood cell count, platelet count, capillary blood glucose at presentation, fasting blood glucose, hemoglobin A1C (HbA1C), lipid profiles, prothrombin time, and INR. Stroke-related data included baseline NIHSS, pre-stroke modified Rankin Scale (mRS), time from onset to treatment, etiologic stroke subtype according to TOAST classification, and identification of hyperdense cerebral artery sign and early infarct signs (defined as any of the following: hypodensity comprising less than one-third of the middle cerebral artery territory, loss of basal ganglia outline, loss of grey-white differentiation, loss of insular ribbon, or effacement of sulci) on baseline CT scan of the brain.

The primary outcome measure was unfavorable functional outcome, defined as mRS score of 3-6 (indicating major disability or death) at three months from stroke onset and symptomatic intracerebral hemorrhage ,defined as a parenchymal hematoma (PH1 or PH2 type), associated with an increase in ≥ 4 points in the NIHSS score.[19]

Statistical analyses were performed using SPSS software version 16.0. Data are presented as means and standard deviations for continuous measures and as counts and percentages for categorical variables. Differences between patients with and without AF were compared using the unpaired t and Wilcoxon rank sum tests for continuous measures and the Fisher exact tests for categorical variables. Unadjusted and adjusted odds ratios (95% CIs) were derived using logistic regression analyses. Statistical significance was considered when $P<0.05$.

The study was approved by the institute's ethical review committee.

Results

We identified 145 patients who were treated with intravenous rtPA during the study period. Four patients were excluded from the statistical analysis: had no follow-up data at 3 months. 141 patients were included in the final analysis. There were 46 (32.62 %) patients had AF.

Baseline demographic and clinical characteristics were reported in Table 1. Among the baseline characteristics, there were six significant factors between those with and without AF (Table 1)

including age, coronary heart disease, Baseline NIHSS at admission and 24 hr. and CT brain findings (hyperdense cerebral artery sign, early infract signs). The AF group had older age than those without AF (66.9 VS 62.4 years), coronary heart disease was significantly higher in the AF group (23.9% VS 8.4%) ,baseline NIHSS score and 24 hr were significantly higher in the AF group (15.7 VS 11.6 ,11.5 VS 6.9), CT brain findings (hyperdense cerebral artery sign, early infract signs) were significantly higher in the AF group (56.5% VS 24.2%, 63% VS 23.2%)

Table 1 Baseline characteristics of acute ischemic stroke patients receiving an rtPA treatment categorized by presence of atrial fibrillation

Factor	Patient with AF (n=46)		Patient without AF (n=95)		P-value
Age (year), mean ± SD	69.9	(11.8)	62.4	(11.9)	0.001
Gender					0.213
Male	22	(47.8)	56	(58.9)	
Female	24	(52.2)	39	(41.1)	
Weight (kg), mean ± SD	64.4	(15.3)	67.8	(11.8)	0.155
Height (cm), mean ± SD	161.3	(9.8)	162.7	(8.7)	0.381
BMI (kg/m^2), mean ± SD	24.1	(3.6)	25.6	(3.9)	0.032
Comorbidity					
Diabetes mellitus	14	(30.4)	32	(33.7)	0.700
Hypertension	37	(80.4)	64	(67.4)	0.107
Dyslipidemia	26	(56.5)	63	(55.8)	0.935
Coronary artery disease	11	(23.9)	8	(8.4)	0.012
Old CVA	3	(6.5)	4	(4.2)	0.554
Atrial fibrillation					
New onset of AF	15	(32.6%)			
Chronic	31	(67.4%)			
Stroke characteristic					
NIISS at admission mean ± SD	15.7	(6.5)	11.6	(5.4)	<0.001
NIHSS at 24 hr, mean ± SD	11.5	(7.8)	6.9	(7.0)	0.001
Cardioembolic stroke	44	(95.7%)	3	(3.2%)	<0.001
Onset to team, SD	122.7	(66.3)	125.8	(69.8)	0.805
Brain imaging					
Hyperdense cerebral artery sign	26	(56.5%)	23	(24.2%)	<0.001
Early infarct signs	29	(63%)	22	(23.2%)	<0.001
Investigation, mean ± SD					
Hb (g/dl)	12.7	(1.2)	13.5	(2.0)	0.002
WBC (cells/mm)	7539.1	(2169.0)	9829.2	(11731.5)	0.192
Platelet(/mm)	213652.2	(63544.6)	248884.2	(65496.3)	0.003
PT (second)	0.007	(1.6)	12.1	(1.8)	13.0
INR	1.1	(0.1)	1.1	(1.2)	0.885
Serum glucose at presentation	149.4	(71.2)	162.7	(87.0)	0.369
FBS (mg/dl)	133.2	(41.4)	141.7	(68.0)	0.36
HbAIC	6.5	(1.6)	67	(2.1)	0.593
Cholesterol (mg/dl)	178.9	(46.1)	197.9	(49.1)	0.031
LDL (mg/dl)	113.4	(37.5)	129.9	(43.9)	0.032

Table 2 Outcome of acute ischemic stroke patients receiving an rtPA treatment

Outcome	Patient with AF (n=46)		Patient without AF (n=95)		P-value
Symptomatic ICH	21	(45.7%)	11	(11.6%)	<0.001
Poor functional outcome	33	(71.7%)	31	(32.6%)	<0.001

Table 3 Multiple logistic regression showing variables associated with symptomatic ICH with IV PA treatment.

Factor	Crude OR	95% CI of Adj.OR		P-value	Adjusted OR	95% CI of Adj.OR		P-value
		Lowe	Upper			Lowe	Upper	
Age (year)	1.06	1.02	1.10	0.004	1.03	0.99	1.07	0.189
NIHSS score at admission	1.14	1.06	1.22	<0.001	1.09	1.01	1.17	0.032
Atrial fibrillation	6.42	273	15.09	<0.001	4.21	1.69	10.51	0.002

Table 4 Multiple logistic regression showing variables associated with unfavorable outcome with IV rtPA treatment.

Factor	Crude OR	95% CI of Adj.OR		P-value	Adjusted OR	95% CI of Adj.OR		P-value
		Lowe	Upper			Lowe	Upper	
Age (year)	1.07	1.03	1.10	<0.001	1.04	1.01	1.08	0.021
NIHSS score at admission	1.23	1.14	1.34	<0.001	1.21	111	1.31	<0.001
Atrial fibrillation	5.24	2.42	11.34	<0.001	3.08	1.27	7.48	0.013

Table 5 MRS at 90 days between chronic AF and new AF

AF	N	MRS at 90 days		P-value
		mean	SD	
Chronic AF	32	3.75	2.02	0.677
New AF	15	3.47	2.45	

Table 6 Shows the mean CHAD2VAS score according to treatment outcomes

Outcome	N	CHAD2VAS score		P-value
		mean	SD	
Symptomatic ICH				
No	25	3.52	0.82	0.008
Yes	22	4.23	0.92	
Poor functional outcome				
No	13	3.00	0.82	<0.001
Yes	34	4.18	0.76	

Regarding stroke outcomes (Table 2). Patients with AF had a higher incidence of symptomatic ICH and a unfavorable functional outcome compared with those without AF. The incidence of symptomatic ICH was significantly higher in patients with AF than in patients without AF (47.5% vs 11.6%), and the incidence of poor functional outcome (modified Rankin Scale score>2) was significantly higher in patients with AF than in patients without AF (71.7% vs 32.6%). The increase risk of symptomatic intracerebral hemorrhage among patients with AF remained significant after adjusting for age and baseline NIHSS (odds ratio, 4.21 [95% CI, 1.69-10.51]) (Table 3). The increase risk of unfavorable outcome among patients with AF remained significant after adjusting for age and baseline NIHSS (odds ratio, 3.08 [95% CI, 1.27 -7.48]) (Table 4).

There were no differences in outcomes between patients with a first-detected episode of AF and patients with chronic AF (Table 5). Patients with AF who had CHA_2DS_2-VASc Score>3 had a higher incidence of symptomatic ICH and unfavorable functional outcome compared with those who had CHA_2DS_2-VASc Score ≤3 (Table 6).

Discussion

This study in acute ischemic stroke patients who were treated with IV rtPA at the Faculty of Medicine Vajira Hospital shows that 46 (32.62 %) patients had AF. Stroke patients with AF were older, more cerebrovascular risk factors and more severe strokes, and their neurological outcome was worse than in patients without AF. In our study, we observed that patients with AF have a significant increase in the risk of symptomatic ICH or unfavorable functional outcome following IV rtPA treatment. Patient with AF, risk of symptomatic ICH was 4.21 times greater in patients without AF. (Adjusted OR = 4.21, 95% CI: 1.69-10.51, P-value = 0.002) and unfavorable functional outcome was 3.08 times greater in patients without AF. (Adjusted OR = 3.08, CI: 1.27-7.48, P-value = 0.013). Our findings are consistent with those of previous studie[20-22] that observed a significant increase in the risk of symptomatic ICH or unfavorable functional outcome among patients with AF treated with rtPA. One study[20] reported that patients with AF were 3 times more likely than patients without AF to have unfavorable functional outcome. Two other studies[21,22] found significant associations between AF and unfavorable functional outcome on univariate, but not on multivariable, analyses. One study in Thailand[23] found significant associations between AF and intracerebral hemorrhage but there was no significant poor functional outcome rate between both groups. These findings, however, appear to conflict with those of another study[24] (which enrolled fewer and younger patients) that reported the lack of such differences between patients with and without AF. The authors suggest that the clinical outcome after thrombolysis (at day 90 as assessed by mRS) and intracerebral hemorrhage may be influenced by the fact that patients with AF have more severe strokes with significantly higher baseline NIHSS and larger infract (Table 1). Patients with AF and embolic arterial occlusion may probably have poorer collateral flow at the time of occlusion onset compared to those with atherothrombotic types of occlusions characterized by a progression of severe stenosis to occlusion causing higher infarct volumes and blood brain barrier disruption and intracerebral hemorrhage.

There were no differences in outcomes between patients with a first-detected episode of AF and patients with chronic AF. Patients with AF who had CHA_2DS_2-VASc Score>3 had a higher incidence of symptomatic ICH and unfavorable functional outcome compared with those who had CHA_2DS_2-VASc Score ≤3. Our findings are consistent with those of previous studies[25,26] that observed the increased CHA_2DS_2-VASc scores in patients with AF are associated with increased NIHSS scores and worse clinical outcome.

This study had several limitations. First, the retrospective design of the study could have inherent biases. Second, the sample size is relatively small and may have insufficient statistical power to demonstrate association of some variables with unfavorable functional outcome.

Conclusion

In conclusion, our study demonstrated that Patients with AF had significantly a higher incidence of symptomatic ICH and a unfavorable functional outcome after intravenous thombolysis when compared to those without AF, probably due to the more severe baseline NIHSS and large infract.

Patients with AF who had CHA_2DS_2-VASc Score>3 had a higher incidence of symptomatic ICH and unfavorable functional outcome compared with those who had CHA_2DS_2-VASc Score ≤3, due to the increased CHA_2DS2-VASc scores are associated with increased NIHSS scores and worse clinical outcome.

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