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Thrombolysis in ischaemic stroke in rural North East Thailand by neurologist and non-neurologists

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Abstract

Background & Objective: Acute ischemic stroke (AIS) has been shown to be effectively treated with thrombolytic therapy. Thailand and other developing countries have limited stroke specialists to prescribe this treatment. Data regarding stroke outcomes in AIS patients who received thrombolytic therapy prescribed by neurologists compared with non-neurologists are limited. *Methods:* This was a large, multicenter, retrospective study conducted in 9 hospitals across the northeastern part of Thailand. The inclusion criteria were AIS patients who were admitted and treated with thrombolytic therapy between January 2010 and December 2012. Patients were categorized into two groups by physician specialty; neurologist and non-neurologist. Clinical outcomes and in-hospital mortality were compared between the groups. *Results:* There were 915 AIS patients who participated in the study; 175 patients were treated by the non-neurologists (19.1%). The mean age of all patients was 64 years and 55.1% were men. The median onset to needle time in both groups were similar at 180 minutes. The National Institutes of Health Stroke Scale (NIHSS) at discharge were significantly higher in neurologist group than non-neurologist group (NIHSS 6 vs 3, p value 0.03). The in-hospital mortality was also higher in neurologist group (9.5% vs 4.0%; p value 0.02).
Conclusions: Non-neurologists may be able to thrombolyze AIS patients safely and effectively.

INTRODUCTION

Stroke is a major health problem worldwide. Acute ischemic stroke (AIS) is the most common subtype of stroke. The estimated prevalence of stroke among adults older than 45 year is 1.88%.[1] Thrombolytic therapy with recombinant tissue plasminogen activator (rtPA) is the standard treatment for AIS. Intravenous rtPA within 4.5 hours after symptom onset is efficacy proven in AIS.[2,3] The outcome was favorable by 28% if rtPA was given compared with placebo.[3]

Thrombolytic therapy has been used in Thailand for over 20 years but in 2010 the overall rtPA therapy in AIS patients in Thailand was still only 1.05%. Most of the patients received rtPA in tertiary and university hospitals.[4] One reason for low rtPA use in Thailand is that the limited numbers of neurologists particularly in the rural area. The ratio of neurologist to population was 1: 1,429,512 people in the Northeastern, Thailand, while this ratio was 1:39,385 people in Bangkok, the capital city. To cope with the limited number of neurologists, the stroke network project was established in 2010. This project assists the non-neurologists in community and secondary hospitals in the treatment of AIS with rtPA. The neurologists at the main server hospitals such as university hospitals function as consultants by telephone and mobile application for communication for the client hospitals in their service area. The project also supports the client hospitals in terms of setting up comprehensive stroke units and referral systems. A previous study from Australia showed that the stroke outcomes were comparable between neurologists and non-neurologists prescribing thrombolytic therapy in

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49 AIS patients.[5] In 2015 AHA/ASA has published update guideline on endovascular treatment of ischemic stroke, and strongly recommend patient with occlusion of internal carotid or proximal (M1) middle cerebral artery, which treatment to initiate within 6 hours of symptoms onset.[6] However this neurointervention procedure can be performed only in one university hospital across the northeastern of Thailand since 2016. This study aimed to evaluate the clinical outcomes of thrombolytic therapy by neurologists and non-neurologists in multi-stroke centers across the Northeastern, Thailand and in a larger study population.

METHODS

The study is a retrospective, cross-sectional study. There were 915 patients with AIS who were treated with rtPA in 9 hospitals across the northeastern of Thailand. The study period was between January 2010 and December 2012.

Data were extracted from the admission records. Demographic variables, clinical characteristics and treatment outcomes were obtained. Stroke subtypes were classified with the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.[7] The admission, 24-hours status and discharge outcomes by the National Institutes of Health Stroke Scale (NIHSS) were recorded.

There were four different types of hospitals classified as university serviced hospitals; tertiary hospitals, secondary hospitals, and primary hospitals as shown in Table 1. Neurologists prescribed rtPA treatment for AIS patients in the first two hospital types while the non-neurologists prescribed in the latter two types of hospitals. Non-neurologist in this study are internist. The main clinical outcome in this study was in-hospital mortality.

Statistical analysis

Baseline characteristics are shown as absolute numbers and percentage for categorical variables; mean and standard deviation (SD) for normally-distributed continuous variables; and median and interquartile ranges for non-normally-distributed continuous variables.

To compare the variables between two groups classified by in-hospital mortality, the Student t-test and Wilcoxon-Man-Whitney U test were used for continuous variables; Chi-square and Fisher's exact tests for categorical variables when appropriate.

Univariate logistic analysis was calculated in all variables associated with in-hospital mortality. Factors with p values less than 0.20 by univariate logistic analysis were included in subsequent multivariate logistic regression models to identify independent predictors for in-hospital mortality. Statistical analyses were performed using STATA software version 10 (College Station, Texas, USA).

RESULTS

During the study period, 915 patients were enrolled in the study. Of those, 175 patients

Table 1: Character of hospitals and numbers of patients who participated in the study from each hospital

Hospital Level	Hospital Name	Hospital size, bed	Treatment by	n (%)
University Hospital	Srinagarind Hospital	1,007	Neurologist	282 (30.8)
Tertiary Hospital	Supphasit hospital	1,000	Neurologist	20 (2.2)
	Maharat Nakhonratchasima hospital	1,019	Neurologist	350 (38.3)
	Khonkaen hospital	867	Neurologist	88 (9.6)
Secondary Hospital	Nakhonphanom hospital	345	Non-Neurologist	33 (3.6)
	Chaiyaphum hospital	550	Non-Neurologist	19 (2.1)
	Kalasin hospital	505	Non-Neurologist	28 (3.1)
	Loei hospital	402	Non-Neurologist	55 (6.0)
Primary hospital	Chumphae hospital	120	Non-Neurologist	40 (4.4)
Total				915 (100)

were treated by the non-neurologists (19.1%). Baseline clinical data and laboratory findings between those who treated with neurologists and non-neurologists were mostly comparable (Table 2 and 3). Those treated by the neurologists had a higher proportion of atrial fibrillation (23.1% vs 10.3%), valvular heart disease (8.8% vs 2.9%), history of transient ischemic attack (2.5% vs 0%), history of stroke (16.0% vs1.2%), and cardioembolism (24.7% vs 10.8%) than those treated by the non-neurologists (Table 2). The neurologist group had a shorter door to needle time period than the non-neurologist group (60 vs 65 minutes; p value 0.02). The initial and discharge NIHSS scores and length of stay of the neurologist group were significantly higher than the non-neurologist group (Table 3). The mortality rate in the neurologist group was also higher than the non-neurologist group (9.5% vs 4.0%) as shown in Table 3.

The overall in-hospital mortality rate was 8.4% (77 patients). There were six factors significantly associated with in-hospital mortality by univariate analysis including hypertension, coronary artery disease, atrial fibrillation, previous stroke, treatment by the non-neurologists, and stroke severity (Table 4). After adjustment, there were five independent factors associated with in-hospital mortality including hypertension, dyslipidemia, coronary artery disease, cardioembolic stroke, and severe stroke. The adjusted odds ratios and 95% confidence intervals of these factors were 2.56 (1.44-4.55), 0.43 (0.19-0.95), 2.52 (1.12-5.69), 0.46 (0.22-0.98), and 7.13 (2.06-34.76). Physician specialty was not related with in-hospital mortality (p-value 0.17).

DISCUSSION

Prior to the thrombolytic era, stroke may have been best managed by neurologists.[8,9] Out of 146 AIS patients, the unadjusted mortality rate for stroke-related causes was significantly lower at six months if treated by neurologists compared with other specialists (4.6% vs 17.2%; p value 0.024).[9] After being adjusted for other confounders, however, the 180 day mortality was not significantly different between neurologists and others (adjusted odds ratio of 0.41 with 95% confidence interval of 0.16-1.05).

At present, it is an era of thrombolytic therapy. Two small studies showed that thrombolytic therapy may be prescribed by either emergency physicians or non-neurologist stroke physicians other than stroke specialists with comparable outcome.[5,9] The study from the US conducted on 43 AIS patients who received thrombolytic therapy prescribed by stroke specialists in 20 patients, and by emergency physicians with phone consultation in 23 patients. Stroke outcomes and complications

Table 2: Baseline characteristics of acute ischemic stroke patients who received thrombolytic therapy categorized by specialty of physicians

Characteristic	Neurologist (n=740)	Non-Neurologist (n=175)	Total (n=915)	p-value
Age, yr (mean ± SD)	64.1 (13.2)	63.9 (12.9)	64.1 (13.1)	0.89
Male sex (%)	411 (55.5)	93 (53.1)	504 (55.1)	0.61
Weight, kg (mean ± SD)	58.8 (12.7)	57.2 (10.6)	58.4 (12.3)	0.13
Hypertension (%)	348 (47.0)	74 (42.3)	422 (46.1)	0.27
Dyslipidemia (%)	125 (16.9)	20 (11.5)	145 (15.9)	0.08
Diabetes (%)	151 (20.4)	34 (19.5)	185 (20.2)	0.83
Coronary artery disease (%)	47 (6.4)	11 (6.3)	58 (6.3)	1.00
Atrial fibrillation (%)	171 (23.1)	18 (10.3)	189 (20.7)	< 0.01
Valvular heart disease (%)	65 (8.8)	5 (2.9)	70 (7.7)	< 0.01
History of TIA (%)	18 (2.5)	0 (0)	18 (2.0)	0.03
History of stroke (%)	118 (16.0)	2 (1.2)	120 (13.2)	< 0.01

TIA, transient ischemic attack.

Table 3: Clinical characteristic, stroke subtype, treatment parameters, and stroke outcomes after thrombolytic therapy categorized by specialty of physicians

Variables	Neurologist (n=740)	Non-Neurologist (n=175)	Total (n=915)	P-value
Systolic pressure, mmHg (median)	149 (132-167)	144 (128-167)	147 (131-167)	0.09
Diastolic pressure, mmHg (median)	83 (73-94)	80 (70-92)	83 (72-93)	0.07
Blood sugar, mg/dl (median)	116 (97.50-148)	115 (97-149)	116 (97-148)	0.69
Cholesterol, mg/dl (median)	181 (152-218)	186 (164-210)	181 (153-217)	0.40
Triglyceride, mg/dl (median)	116 (93-152)	105 (79.50-153)	116 (90-152)	0.10
LDL, mg/dl (median)	109 (86-140)	117 (99-140)	110 (88-140)	0.05
HDL, mg/dl (median)	46 (38-56)	43.5 (37-56)	46 (38-56)	0.30
TOAST classification				< 0.01
Large-artery atherosclerosis (%)	228 (35.0)	36 (43.4)	264 (35.9)	
Small vessel occlusive disease (%)	260 (39.9)	36 (43.4)	296 (40.3)	
Cardioembolism (%)	161 (24.7)	9 (10.8)	170 (23.1)	
Others determined etiology (%)	0 (0)	0 (0)	0 (0)	
Undetermined etiology (%)	3 (0.46)	2 (2.41)	5 (0.68)	
Stroke severity				0.13
Mild (NIHSS 0-6)	106 (16.2)	36 (21.8)	142 (17.4)	
Moderate (NIHSS 7-15)	340 (52.1)	87 (52.7)	427 (52.2)	
Severe (NIHSS 16-42)	207 (31.7)	42 (25.5)	249 (30.4)	
Door to needle, min (median)	60 (46-76)	65 (50-84)	60 (47-78)	0.02
Onset to needle, min (median)	180 (145-220)	180 (138-220)	180 (145-220)	0.60
Initial NIHSS score (median)	12 (8-16)	11 (7-16)	12 (8-16)	0.01
NIHSS score at discharge (median)	6 (2-12)	3 (0.75-10)	5 (1-12)	0.03
Length of stay, day (median)	4 (3-7)	4 (3-6)	4 (3-7)	< 0.01
Death (%)	70 (9.5)	7 (4.0)	77 (8.4)	0.02

HDL, high density lipoprotein; IQR, interquartile range; LDL, low density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack; TOAST, Trial of Org 10172 in Acute Stroke Treatment; data presented as median present with interquartile range.

of thrombolytic therapy were comparable between both groups.[5] Similarly, there was no patient who developed symptomatic intracerebral hemorrhage after thrombolytic therapy was prescribed in 49 AIS patients; 21 patients by neurologist stroke specialists and 28 patients by non-neurologist stroke physicians.[10]

This present study was a large 915 patients, multi-center trial to confirm that non-neurologists may be able to thrombolyze AIS patients safely and effectively. The NIHSS at discharge in the non-neurologist group were better than the neurologist group as shown in Table 3. One possible explanation for this finding was that there were more severe patients in neurologist group (31.7% vs 25.5%). The in-hospital mortality rate was even higher and statistically significant in neurologist group compared to the non-neurologist group (9.5% vs 4.0%; p value 0.02) as shown in Table 3. These findings were similar to the study from Australia in which the in-hospital mortality for stroke specialists was higher than non-neurologist stroke physicians (10% vs 7%).[10] Note that there is no stroke specialist in Northeastern Thailand; only neurologists and internists who can prescribe thrombolytic therapy. Additionally, the median onset to needle times in both groups was similar at 180 minutes (Table 3).

There were five independent factors associated with in-hospital mortality but not with physician specialist (p value 0.17) as shown in Table 5. Hypertension, coronary artery disease, and severe stroke were associated with higher AIS death in hospital, while dyslipidemia and cardioembolic stroke were associated with lower death. Hypertension was a strong risk factor for stroke[11], while presence of coronary artery disease was an indicator of atherosclerosis.[9] A previous study showed an association of cardiac disease and high mortality in AIS stroke patients , with

Table 4: Univariate analysis of factors associated with in-hospital mortality in acute ischemic stroke patients received thrombolytic therapy

Factors		Death (%)	Alive (%)	Crude odds ratio (95% CI)
Age	Age < 40	4 (7.7)	48 (92.3)	1.0
	Age 41 -50	4 (4.5)	84 (95.5)	0.57 (0.13-2.38)
	Age 51-60	11 (6.0)	172 (94.0)	0.76 (0.23-2.51)
	Age 61-70	17 (6.4)	247 (93.6)	0.82 (0.266-2.56)
	Age 71-80	31 (12.4)	220 (87.6)	1.69 (0.57-5.01)
	Age >80	10 (13.9)	62 (86.1)	1.94 (0.57-6.55)
Sex	Male	44 (8.7)	460 (91.3)	1.0
	Female	33 (8.0)	378 (92.0)	0.91 (0.57-1.46)
Risk factors	Hypertension	51 (12.1)	371 (87.9)	2.47 (1.51-4.04)
	Dyslipidemia	10 (6.9)	135 (93.1)	0.77 (0.38-1.54)
	Diabetes	16 (8.6)	169 (91.4)	1.03 (0.58-1.84)
	Coronary artery disease	10 (17.2)	48 (82.8)	2.45 (1.18-5.06)
	Atrial fibrillation	27(14.3)	162 (85.7)	2.25 (1.36-3.70)
	Valvular heart disease	10 (14.3)	60 (85.7)	1.93 (0.94-3.94)
	History of TIA	0 (0)	18 (100)	n/a
	History of stroke	16 (13.3)	104 (86.7)	1.88 (1.04-3.38)
Treatment by	Neurologist	70 (9.46)	670 (90.54)	1
	Non-neurologist	7 (4.0)	168 (96.0)	0.39 (0.18-0.88)
Stroke subtype (TOAST)	Large artery atherosclerosis	34 (12.9)	230 (87.1)	1
	Small vessel occlusion	24 (8.1)	272 (9.1.9)	0.59 (0.34-1.03)
	Cardioembolism	16 (9.4)	154 (90.6)	0.70 (0.37-1.31)
	Undetermined	0 (0)	5 (100)	0.00
Onset to needle time	< 180 min	34 (8.0)	389 (92.0)	1
	180-270 min	43 (9.0)	435 (91.0)	1.13 (0.70-1.81)
Stroke severity	Mild (NIHSS 0-6)	3 (2.1)	139 (97.9)	1
	Moderate (NIHSS 7-15)	30 (7.0)	397 (93.0)	3.50 (1.05-11.65)
	Severe (NIHSS 16-38)	42 (16.9)	207 (83.1)	9.40 (2.85-30.92)

NIHSS indicates National Institutes of Health Stroke Scale; TIA, transient ischemic attack; TOAST Trial of Org 10172 in Acute Stroke Treatment; n/a: not available.

an adjusted odds ratio of 7.36 (95% confidence interval of 1.60-33.90).[1,9] Severe strokes were also associated with a higher mortality than less severe strokes.[7]

AIS patients with dyslipidemia and cardioembolic stroke tended to have lower in-hospital mortality in this study. These may be explained by the quite low LDL-C level in the overall of this study. The median LDL-C level was only 110 mg/dL (Table 3), which indicated that many or most patients may have received statin therapy prior to stroke development. Cardioembolic stroke particularly in patients with atrial fibrillation usually had poor stroke outcomes.[11,12] The in-hospital mortality in AIS with atrial fibrillation was 14.1% compared with 6.2% without atrial fibrillation.[11] In this study, valvular heart disease accounted for 7.1% of all patients. These patients were mostly young and had rheumatic heart disease which was prevalent in the northeastern Thailand. The prognosis in these patients may be better than those AIS patients with atrial fibrillation and in the older age group.

One possible explanation for the differences of AIS treatment outcomes between the neurologists and non-neurologists was the confidence of attending physicians. The non-neurologists have only attended a short course or workshop of the stroke treatment. Therefore, they tended to refer severe stroke patients to the center or tertiary

Table 5: Multivariate logistic regression model of factors associated with in-hospital mortality in acute ischemic stroke patients received thrombolytic therapy

Factors		Adjusted odds ratio	95% confidence interval	p-value
Age	Age < 40	1		
	Age 41 - 50	0.71	0.17 – 3.05	0.65
	Age 51 - 60	0.47	0.13 – 1.80	0.27
	Age 61 - 70	1.35	0.42 – 4.32	0.61
	Age 71 - 80	1.12	0.33 – 3.73	0.86
	Age > 80	1.38	0.37 – 5.09	0.63
Sex	Male	1		
	Female	0.88	0.52 – 1.52	0.66
Risk factors	Hypertension	2.56	1.44 - 4.55	< 0.01
	Dyslipidemia	0.43	0.19 - 0.95	0.04
	Diabetes	0.73	0.36 – 1.46	0.37
	Coronary artery disease	2.52	1.12 - 5.69	0.03
	Atrial fibrillation	1.76	0.92 – 3.35	0.09
	Valvular heart disease	0.88	0.37 – 2.09	0.78
	Previous stroke	1.49	0.78 – 2.85	0.22
Treatment by	Non-neurologist	1		
	Neurologist	0.60	0.29 – 1.24	0.17
Stroke subtype (TOAST)	Large-artery atherosclerosis	1		
	Small vessel occlusive disease	0.62	0.33 – 1.18	0.15
	Cardioembolism	0.46	0.22 - 0.98	0.04
Onset to needle time	< 180 min	1		
	180-270 min	0.99	0.59 – 1.67	0.97
Stroke severity	Mild (NIHSS 0-6)	1		
	Moderate (NIHSS 7-15)	3.12	0.91 – 10.78	0.07
	Severe (NIHSS 16-38)	7.13	2.06 – 24.76	< 0.01

NIHSS indicates National Institutes of Health Stroke Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

care hospitals resulting in more severe cases in the neurologist group. However, in this study we were unable to identify the numbers of referred patients in the neurologist group.

There are some limitations in this study. Due to the retrospective study design, no long term mortality or functional outcome data were recorded. Data regarding complications of thrombolytic therapy such as intracerebral hemorrhage were limited. Numbers of patients in both groups were not equal due to different sizes of the catchment area of each hospital. Finally, the neurologist group had more patients with severe stroke (31.7% vs 25.5%) than the non-neurologist group. These last two limitations may be solved by multivariate logistic regression analyses. Even though the non-neurologists seemed to have lower mortality rate by univariate analysis, it is not statistically significant by multivariate analysis. Other factors such as hypertension or stroke subtype were more important than specialty of rtPA prescribers. Neurologists may have more skills in stroke care than non-neurologists. Note that the experience of non-neurologist physicians were not studied such as seniority of non-neurologists compared to neurologists, cumulative experience, or the overall total number of strokes seen per year of the attending physicians in both groups. This study included only AIS patients who received rtPA treatment. Those who were considered for thrombolysis but excluded due to numerous contraindications were not studied. Therefore, the results of this study may not apply for all AIS patients.

In conclusion, non-neurologists may be able to thrombolyze in AIS patients safely and effectively.

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