Time intervals and in-hospital delay in thrombolysis administration in acute ischemic stroke

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ABSTRACT

OBJECTIVE
To determine the time intervals at the Emergency Department (ED) resulting in delayed thrombolytic therapy.

METHODS
This was a cross-sectional analytical study including 268 stroke fast track patients who admitted at ED of Khon Kaen Hospital, Thailand. Period of time for each patient was assessed before received thrombolytic drug. Door to needle (DTN) time more than 60 minutes was considered a delayed treatment. Time intervals that impact DTN time and accuracy of prediction were analyzed.

RESULTS
Of 88 with thrombolysis administration, there were 51 patients in the delayed group and 37 patients in the non-delayed group. The median DTN time was 75 minutes (interquartile range (IQR), 68 to 84) in the delayed group and 55 (IQR, 48 to 58) minutes in the non-delayed group. Final test to needle (FTN) time was the time interval that affected delayed treatment (adjusted odds ratio, 2.63; 95% confidence interval [CI], 1.33 to 5.13; P=0.005) and FTN time 34 minutes or longer had prognostic performance 90.4% (95% CI, 84.2 to 96.5), sensitivity 76.5% (95% CI, 62.5 to 87.2) and specificity 94.6% (95% CI, 81.8 to 99.3) to predict delayed thrombolysis administration.

CONCLUSION
In adults with acute ischemic stroke, FTN 34 minutes or longer was associated with the delay in thrombolysis administration.

INTRODUCTION

Stroke is the second cause of death in the population over the age of 60 years worldwide, people around the world die each year of stroke about 6 million people, and about 5 million people are permanent disabilities.[1] Its standard and the most acceptable treatment is thrombolytic therapy, starting drug early and within 4.5 hours since the onset of symptoms can improve outcome.[2-5] American Stroke Association has set the time frame of various processes as follows: the patients should receive a brain imaging within 25 minutes, interpreted by a specialist within 45 minutes and received thrombolytic drug within 60 minutes.[6] However, it is still found that most patients with acute ischemic stroke still do not receive the drug within the specified time.[7,8] There are studies regarding factor associated with an in-hospital delay in intravenous thrombolysis for acute ischemic stroke that focused on patient and hospital characteristics.[9-13] There is, however, limited study about time intervals before receiving the drug. Therefore, this study aimed to determine the time factors and treatment process for patients with acute ischemic stroke within the Emergency Department (ED) resulting in the delayed thrombolytic drug.

METHODS

PATIENTS AND OVERSIGHT

From January through December 2017, the cross-sectional analytical study was conducted at the ED, Khon Kaen Hospital, Thailand. All patients who presented with clinical signs of acute ischemic stroke which consists of slurred speech, arm weakness, face drooping, one or the other with symptoms, not more than 3 hours (stroke fast track, SFT) and 18 to 80 of age were eligible for the study. Criteria for exclusion were the duration of onset of symptom until receiving the thrombolytic drug was more than 270 minutes (4.5 hours) and incomplete time record data. The study was approved by the research ethics board of Khon Kaen Hospital, it was designed by the author and no industry support or funding. The results were collected and analyzed by the author, who vouch for the data.

IN-HOSPITAL STROKE FAST TRACK PROTOCOL

The processes when the stroke fast track patients arrived at the ED included an assessment by an emergency physician, informing the neurologist, sending the blood to test in laboratory examination, using brain imaging for the diagnosis of brain ischemia. The indications and contraindications were considered for giving thrombolytic drug and requesting consent from patients and relatives.

VARIABLES

The patient characteristics including age, sex, medical history i.e., diabetes mellitus, hypertension, dyslipidaemia, atrial fibrillation, prior stroke, current smoking and heavy drinking, baseline variables i.e., systolic blood pressure (SBP), diastolic blood pressure (DBP), blood sugar and National Institute of Health Stroke Scale (NIHSS); type of presenting including on their

Table 1. Characteristics of the patients

Characteristic	Delayed door to needle time (n=51)	Non-delayed door to needle time (n=37)
Age, median (IQR), years	68 (61-75)	60 (56-73)
Male-no. (%)	32 (62.8)	19 (51.4)
Medical history-no. (%)		
Diabetes mellitus	16 (31.4)	14 (37.8)
Hypertension	26 (51.0)	21 (56.8)
Dyslipidemia	5 (9.8)	3 (8.1)
Atrial fibrillation	9 (17.6)	14 (37.8)
Hypertension	1 (2.0)	2 (5.4)
Current smoking	7 (13.8)	2 (5.4)
Heavy drinking	5 (9.8)	5 (13.5)
Baseline variables, median (IQR)-mmHg		
Systolic blood pressure	159 (139-173)	154 (136-170)
Diastolic blood pressure	88 (78-98)	91 (76-103)
Blood sugar	132 (104-162)	130 (107-161)
National Institute of Health Stroke Scale	10 (7-14)	12 (8-16)
Type of presenting -no. (%)		
On their own	6 (11.8)	4 (10.8)
Emergency Medical Service	8 (15.7)	7 (18.9)
Referred from other hospitals	37 (72.5)	26 (70.3)
Working day -no. (%)	33 (62.8)	24 (64.9)
Time of presenting -no. (%)		
8.00-16.00	29 (56.9)	27 (73.0)
16.00-24.00	18 (35.3)	10 (27.0)
00.00-8.00	4 (7.8)	0 (0.0)

Table 2. Treatment outcomes

Outcome	Delayed door to needle time (n=51)	Non-delayed door to needle time (n=37)
Intracerebral hemorrhage-no. (%)	4 (7.8)	9 (24.3)
Brain herniation -no. (%)	11 (21.6)	8 (21.6)
Craniectomy -no. (%)	4 (7.8)	2 (5.4)
Death -no. (%)	6 (11.8)	5 (13.5)

own, Emergency Medical Service (EMS), refer; day and time of presenting; outcome including intracerebral hemorrhage, brain herniation, undergo craniectomy and dead were analyzed.

The time from symptom onset to administration of the thrombolytic drug was divided into the following intervals: the duration from the symptom onset to ED (onset to door, OTD), the duration from arrival at ED to evaluation by doctor (door to evaluation, DTE), the period from the arrival at ED until the blood was sent for laboratory examination (door to laboratory, DTL), the period from the arrival at the ED until receiving computerized brain tomography (door to imaging, DTI), the final examination completed (laboratory blood test or brain imaging results) until receiving thrombolytic drug (final test to needle, FTN), the duration of the occurrence of symptom until receiving thrombolytic drug (onset to needle, OTN) and the time since arriving at the ED until receiving a thrombolytic drug (door to needle, DTN).

STATISTICAL ANALYSIS

All calculations were performed using STATA 11.0 software. All analyses were based on comparison

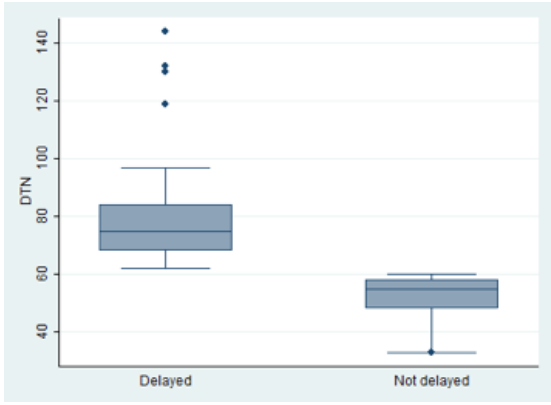

Figure 1. Door to needle times compare between delayed and not delayed group.

between the delayed DTN (>60 minutes) and non-delayed DTN. Quantitative variables were presented as median and interquartile ranges (IQR). Mann-Whitney U test was used to compare median between two groups. Binary logistic regression was used to identify the variables impacting DTN time. The factors that showed significant results in univariate analysis were included in the multivariate analysis, P≤0.05 was considered statistically significant to estimate the crude odds ratios (COR), adjusted odds ratios (AOR) and 95% confidence interval (CI). The accuracy, sensitivity, specificity with 95% CI were also analyzed using the receiver operating characteristic (ROC) curve to find the best cut-off points of the time interval.

RESULTS

There were 1,129 patients with acute ischemic stroke, 268 patients were stroke fast track patients and 88 patients received thrombolytic drugs within 270 minutes; 51 in the delayed group

Table 3. Times intervals

Time interval-min	Delayed door to needle time (n=51)	Non-delayed door to needle time (n=37)	P Value
	Median (IQR)		
Onset to door	120 (85-155)	157 (120-189)	0.002
Door to evaluation	2 (0-7)	2 (0-5)	0.734
Door to laboratory	9 (5-14)	9 (7-11)	0.855
Door to imaging	24 (18-29)	20 (17-22)	0.024
Final test to needle	37 (34-46)	22 (15-25)	<0.001
Door to needle	75 (68-84)	55 (48-58)	<0.001
Onset to needle	202 (165-225)	213 (175-242)	0.323

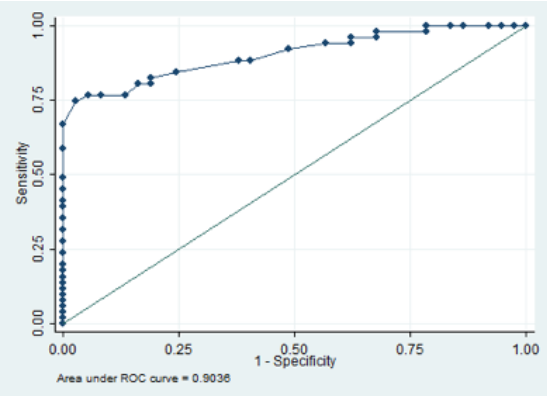

Figure 2. Receiver operating characteristic (ROC) curve for final test to needle (FTN) time ability to predict the delay in thrombolysis administration

and 37 in the non-delayed group. The characteristics of these 88 patients are shown in Table 1. Most of them were male with a median age of more than sixty years old. Generally, their characteristics were similar.

The number of patients with intracerebral hemorrhage after thrombolysis administration were more in the non-delayed group (Table 2). There were a similar numbers of death in both groups, all of them died from severe sepsis.

From the analyzing of various time factors comparing between the delayed and non-delayed group, it was found that the former tended to have shorter OTD (P=0.002) but longer DTI (P=0.024), longer FTN (P<0.001), and longer DTN (P<0.001) (Table 3).

From Table 4, it was found that longer OTD, DTI, and FTN were associated with the delay in thrombolysis administration (COR, 0.88; 95% CI, 0.77 to1.00, P=0.043; COR, 1.07; 95% CI, 1.01 to1.13, P=0.023; and COR, 1.22; 95% CI, 1.12 to1.33, P<0.001, respectively) from the univariable analysis. However, when the three periods were included in the binary logistic regression, it was found that only FTN was significantly associated with the delay in thrombolysis administration

Table 4. The association between time intervals and the delay in thrombolysis administration.

Variables	Crude odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
Onset to door-min	0.88 (0.77-1.00)	0.98 (0.95-1.02)
Door to imaging-min	1.07 (1.01-1.13)	0.93 (0.69-1.25)
Final test to needle-min	1.22 (1.12-1.33)	2.63 (1.33-5.18)

(AOR, 2.63; 95% CI, 1.33 to 5.18, P=0.005) while OTD and DTI were not.

When bringing the FTN period to computing the ROC curve, it was found that the duration from 34 minutes or more had prognostic performance 90.4% (95% CI, 84.2 to 96.5), sensitivity 76.5% (95% CI, 62.5 to 87.2) and specificity 94.6% (95% CI, 81.8 to 99.3) to predict the delay in thrombolysis administration (Figure 2).

DISCUSSION

In acute ischemic stroke patients with indications for treatment and no contraindications for the thrombolytic drug, the faster treatment indicate the better response and the reduction of complications. The present study found that the median DTN period was longer in the delayed group, although OTD period was shorter in the delayed group. This might be less eagerness for those coming early in the present study.

In the present study, FTN was the only factor found to be associated with the delay in thrombolysis administration. This might be due to the fact that this period is the time of the decision to consider the treatment which consists of several sub-processes, such as neurologist consultation, giving information and requesting consent from patients and relatives before prescribing the treatment. These findings were similar to that of the previous cohort study from China in 2015 with 202 patients with acute ischemic stroke, from the linear regression it found that the time interval of FTN greater than or equal to 30 minutes was associated the delay in thrombolysis administration due to the decision process of patients and relatives being concerned about complications from treatment and high drug prices.[14]

However, one retrospective case review from the US in 2017 with 487 patients with acute ischemic stroke with the thrombolysis administration it found that the delay of thrombolysis administration was associated with the delayed imaging.[15] Moreover, it also found that DTI more than 25 minutes was found in about half of the patients.[15] Nonetheless, no study has been made to describe the appropriate time of FTN for prompt thrombolysis administration.

The limitation of the present study included its retrospective in nature. Thus, potential several sub-processes causes of the delayed FTN were unable to unretrievable. Therefore, the further study should focus on the process in the FTN period such as a final test to doctor decision, final test to

the patients' and relatives' decision, final test to drug preparation. It will determine the specific time interval that causes the delay in thrombolysis administration. This study was done in the only one tertiary hospital with the availability of support systems of diagnosis and treatment. Degree of generalization is, hence, limited

In conclusion, the FTN period of less than 34 minutes was associated with prompt thrombolytic administration. Further research with a larger sample and prospective in nature to confirm our findings is needed. Detail of sub-process of FTN should be verified for a better understanding of our care delivery.

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