Original Article

Factors Associated with Poor Clinical Outcome after Intravenous Recombinant Tissue Plasminogen Activator (rt-PA) for Acute Ischemic Stroke in Northeastern Thailand

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Objective: To evaluate the factors associated with poor treatment outcomes of acute ischemic stroke after intravenous recombinant tissue plasminogen activator (rt-PA) therapy from 7 hospitals in Northeastern Thailand.

Materials and Methods: The present study was a retrospective analytical study. Data were obtained from medical records of acute ischemic stroke patients who reached hospital within 4.5 hours after onset and received rt-PA during 2008 May to 2012 April. The authors evaluated time and process to access hospital, duration of treatment process, and factor associated with good and poor clinical outcomes.

Results: During the study period, 778 patients met the study criteria. Mean onset-to-door time was 1.85±1.05 hours. Previous visiting medical center unavailable for rt-PA made patients delay reaching hospitals (OR 1.62 (95% CI 1.28 to 2.04), *p*-value <0.001). Mean onset-to-needle time was 3.08±1.11 hours. Factors leading to poor outcome were atrial fibrillation (AF) (OR 2.38 (95% CI 1.33 to 4.23), *p*-value = 0.003) and onset-to-needle time more than 180 minutes (OR 14.78 (95% CI 7.91 to 27.62), *p*-value <0.001).

Conclusion: Patients came to hospital late because of previously visiting medical centers where rt-PA-was unavailable. Atrial fibrillation and onset-to-needle time more than 180 minutes associated to poor outcome.

Keywords: Poor outcomes, rt-PA, Ischemic stroke

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The gold standard for treatment of acute ischemic stroke is intravenous recombinant tissue plasminogen activator (rt-PA) within 4.5 hours from onset of symptoms. In 2008, stroke fast track system was initiated in Thailand including Srinagarind hospital, Khon Kaen by giving public information and referral development.

There is previous study in Srinagarind Hospital at the beginning of rt-PA era from 1 May 2008 to 31 July 2010. The stroke fast track system was initially set up showing that 75 patients had stroke onset symptoms within 4.5 hours then were given the thrombolysis agent, the mean onset-to-door time was 109 minutes and the mean door-to-needle time was 42 minutes (20 to 67 minutes)[1]. Other data in Thailand showing no difference in the mean door-to-needle time while the mean onset-to-door time were shorter at 65.2 minutes[2]. The study in China showed that factors influencing early healthcare visits were their underlying diseases such as atrial fibrillation and coronary artery disease, alteration of consciousness, ambulance service[3]. The factors causing late healthcare visit consisted of diabetes mellitus, stroke onset at home, clinic visit after onset. Thrombolytic therapy administration within 90 minutes of onset-to-needle time showed better outcome[3]. Therefore, the present study aimed to evaluate time and process to access hospital, duration of treatment process, and factor associated with good and poor clinical outcomes.

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Materials and Methods

The present study was a multicenter retrospective analytical study, conducted at Srinagarind Hospital, Khon Kaen University and other six hospitals in the service area of Public Health section 7 and 8 in Northeastern Thailand; Chumpae Hospital, Ubon Ratchathani Hospital, Nakhon Phanom Hospital, Chaiyaphum Hospital, Kalasin Hospital, and Nakhon Ratchasima Hospital. The study period was

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between May 2008 and April 2012. The inclusion criteria included adult patients diagnosed as acute ischemic stroke who received rt-PA treatment. Those with incomplete data were excluded.

Baseline characteristics and stroke outcomes of all eligible patients were evaluated from the medical record, including the NIH Stroke Scale (NIHSS), modified Rankin Scale (mRS) and Barthel's index (BI). Good outcome was defined as NIHSS 0 to 6 or mRS 0 to 1 at discharge day[4].

Statistical analysis

The present study was an analytical study. All information including demographic data, clinical presentation, transportation, time taken in each step, severity of stroke, treatment outcome, complications and mortality rate were recorded. Data were presented in percentage and mean. Chi-square test or Fisher's exact test was used for comparison of categorical variables and logistic regression for multiple variables. All statistical analyses were computed by the STATA software version 10.0 (College Station, Texas, USA).

Results

During the study period, 807 patients met the study criteria. Of those, 35 patients were excluded due to incomplete data. There remained 772 patients for analysis. The average age was 63±13.2 years. The data showed that most common presentations were motor weakness, facial palsy, and dysarthria, respectively. Other characteristic data were shown in Table 1. Factor causing late arrival was previous visit to an rt-PA unavailable medical center (OR 1.62 (95% CI 1.28 to 2.04), $p<0.001$) (Table 2). The data were collected about processing time from stroke symptoms until rt-PA administration showed that mean onset-to-door time was 1.85±1.05 hours, mean door-to-CT time was 0.39±0.40 hours, mean CT-to-needle time was 0.91±0.57 hours, mean door-to-needle time was 1.30±0.68 hours, and mean onset-to-needle time was 3.08±1.11 hours. The different times of the day could provide fast services similarly (Table 3). The outcome of treatment was good outcome at 65.44%. The underlying factors of patients that affected on treatment were atrial fibrillation (OR 2.38 (95% CI 1.33 to 4.23), p-value = 0.006) and thrombolytic treatment after 180 minutes (OR 14.78 (95% CI 7.91 to 27.62), p-value <0.001) (Table 4).

Table 1. Baseline characteristic of patients

Factors	n (%)
Male	420 (54.4)
Hypertension	378 (48.96)
Dyslipidemia	137 (11.77)
Diabetes mellitus	163 (21.14)
Coronary artery disease	52 (6.74)
Congestive heart failure	11 (2.61)
Atrial fibrillation	177 (22.96)
Valvular heart disease	63 (8.17)
Peripheral arterial disease	2 (0.48)
Transient ischemic attack (TIA)	18 (2.33)
Prior ischemic stroke	118 (15.45)
Smoking	281 (36.43)
Previous antiplatelet therapy	102 (13.19)
Previous statins use	83 (10.74)
Clinical presentations	**n (%)**
Motor weakness	363 (88.32)
Facial palsy	19 (4.62)
Dysarthria	13 (3.16)
Aphasia	9 (2.18)
Sensory deficit	4 (0.97)
Alteration of consciousness	3 (0.73)
Stroke subtypes	**n (%)**
Lacunar stroke	238 (33.47)
Large arterial disease	197 (27.70)
Cardioembolic stroke	146 (20.53)
Others determined	126 (17.72)
Undetermined	4 (0.58)
Stroke score	**Mean (SD)**
At onset NIHSS	2.46 (5.64)
At onset mRS	13.91 (1.22)
At onset BI	45.90 (50.62)
At 24 hr NIHSS	8.18 (17.83)
At discharge day NIHSS	7.77 (6.59)
At discharge day mRS	2.55 (1.91)
At discharge day BI	64.34 (59.39)

Discussion

The mean onset-to-door time was 110 minutes as indistinguishable as the previous study in Srinagarind Hospital from 2008 to 2010 at 109 minutes which was still slower than other hospital at 65.2 minutes[2]. Factors involved with delayed reaching time for rt-PA was previously visiting an unavailable thrombolytic agent's hospital. Symptoms such as hemiparesis, facial drooping, speech difficulty, numbness and alteration of consciousness were main reasons for relatives to bring patients to the hospitals. However, some symptoms usually occurred among elderly patients such as dizziness, gait disturbance, and headache which possibly were ignored by their relatives causing late arrival. Moreover, these symptoms could present as early arrival but may be missed a diagnosis for thrombolytic treatment by physician.

The processing time from stroke symptoms until rt-PA administration showed that different times of the day could provide fast services similarly. The processing time from arrival at the hospital until CT brain scan was 23.4 minutes. However, the processing time from CT brain to thrombolytic treatment was considerably long at 54.6 minutes due to the delay of transferring the patient to the x-ray room and ward, waiting time for blood tests and specialist consultation.

For severity of ischemic stroke, the overall severity was moderate. The outcome of treatment was good outcome at 65.44% compared to the previous study showing at 47%

Table 2. Time to presentation stratified by patients' characteristics and time taken in each step

Factors	Total (%)	Mean onset-to-door time (hr)	*p*-value
Onset situation			
Home	320 (77.94)	1.93±1.03	0.31
Other	91 (22.06)	1.98±1.18	
Time			
6.01 to 12.00	163 (40.09)	1.85±1.04	0.28
12.01 to 18.00	169 (41.03)	1.92±1.01	
18.01 to 6.00	79 (18.88)	1.69±1.16	
Transportation means			
Ambulance	165 (40.05)	2.02±1.41	0.001
Self-transportation	240 (58.50)	1.74±0.88	(OR 1.004 95% CI 1.00 to 1.01)
Unknown	6 (1.45)	-	
Previous visit to rt-PA unavailable medical center			
Yes	153 (37.11)	2.16±1.14	<0.001
No	255 (61.93)	1.65±1.09	(OR 1.62, 95% CI 1.28 to 2.04)
Unknown	3 (0.96)	-	

Table 3. Time taken in each step

Time/time taken in each step (hr)	06.01 to 12.00	12.01 to 18.00	18.01 to 06.00	Average	*p*-value
Onset-to-door time	1.85±1.04	1.92±1.01	1.69±1.16	1.85±1.05	0.28
Door-to-CT time	0.43±0.47	0.35±0.37	0.38±0.27	0.39±0.40	0.16
CT-to-needle time	0.95±0.74	0.87±0.43	0.89±0.40	0.91±0.57	0.50
Onset-to-needle time	3.17±1.08	3.09±1.11	2.91±1.15	3.08±1.11	0.22

of good outcome[5]. Considering the underlying factors of patients that affected treatment, it was found that atrial fibrillation and time to thrombolytic treatment. Atrial fibrillation is associated with poor outcome as shown in previous studies[6]. This condition was preventable with proper treatment before strokes occur.

In conclusion, treatment of acute ischemic stroke by intravenous rt-PA in the present study has good outcome albeit with similar complications as compared with previous studies. However, many patients came to hospital later than in previous studies because of previously having visited rt-PA was unavailable at the medical center. Atrial fibrillation and onset-to-needle time more than 180 minutes leaded to poor outcome.

What is already known on this topic?

An intravenous recombinant tissue plasminogen activator (rt-PA) therapy is beneficial in acute ischemic stroke patients showed by several studies including several Thai studies. However, there is limited data on the reason for late presentation and factor associated with poor clinical outcomes in multicenter study.

What this study adds?

Patients came late to hospital because of previously visiting facility where (rt-PA) was unavailable. Atrial fibrillation and onset-to-needle time more than 180 minutes leaded to poor clinical outcome.

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Potential conflicts of interest

The authors declare no conflict of interest.

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Table 4. Baseline characteristics and outcomes

Medical history	Poor outcome (%)	Good outcom* (%)	*p*-value
Age			
<60 years old	39 (35.14)	72 (64.86)	0.320
60 to 79 years old	65 (36.52)	113 (63.48)	
≥80 years old	7 (22.58)	24 (77.42)	
No history of stroke	106 (34.53)	201 (65.47)	0.501
Previous stroke	8 (42.11)	11 (57.89)	
No history of TIA	112 (36.01)	199 (63.99)	0.054
Previous TIA	2 (12.50)	14 (87.50)	
No anticoagulant therapy	112 (34.67)	211 (65.33)	0.804
Previous anticoagulant therapy	2 (40.00)	3 (60.00)	
No aspirin therapy	93 (36.47)	162 (63.53)	0.250
Previous aspirin therapy	21 (27.87)	52 (73.13)	
No diabetes mellitus	82 (33.47)	163 (66.53)	0.361
Diabetes mellitus	32 (39.02)	50 (60.98)	
No dyslipidemia	89 (33.84)	174 (66.16)	0.432
Dyslipidemia	25 (39.06)	39 (60.94)	
Normotension	59 (36.76)	106 (64.24)	0.702
Hypertension	55 (33.74)	108 (66.26)	
No coronary artery disease	108 (35.64)	195 (64.36)	0.292
Coronary artery disease	6 (25.00)	18 (75.00)	
No atrial fibrillation	88 (31.77)	189 (68.23)	0.0033
Atrial fibrillation	26 (52.00)	24 (48.00)	(OR 2.38, 95% CI 1.33 to 4.23)
Non-valvular atrial fibrillation	19 (51.35)	18 (48.65)	0.521
Valvular atrial fibrillation	28 (58.33)	20 (41.67)	
No valvular heart disease	105 (33.87)	205 (66.13)	0.108
Valvular heart disease	9 (52.94)	8 (47.06)	
No smoking	40 (38.02)	94 (61.98)	0.288
Smoking	73 (28.12)	119 (71.88)	
Onset-to-needle time			
≤180 min	12 (7.22)	154 (92.78)	<0.0001
>180 min	189 (54.46)	158 (45.54)	(OR 14.78, 95% CI 7.91 to 27.62)
Overall	287 (34.56)	505 (65.44)	-

* National Institutes of Health Stroke Scale (NIHSS) 0 to 6 or modified Rankin scale (mRS) 0 to 1 at discharge day were considered to indicate good outcome in the present study
TIA = Transient ischemic attack

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การให้ยาละลายลิ่มเลือดในผู้ป่วยโรคหลอดเลือดสมองขาดเลือดระยะเฉียบพลันในภาคตะวันออกเฉียงเหนือของไทย

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วัตถุประสงค์: เพื่อประเมินปัจจัยที่เกี่ยวข้องกับผลการรักษาที่ไม่ดีในผู้ป่วยโรคหลอดเลือดสมองชนิดขาดเลือดเฉียบพลันที่ได้รับการรักษาด้วยยา recombinant tissue plasminogen activator (rt-PA) ทางหลอดเลือดดำใน 7 จังหวัดของภาคตะวันออกเฉียงเหนือในประเทศไทย

วัสดุและวิธีการ: การศึกษานี้เป็นการศึกษาแบบย้อนหลัง (retrospective analytical study) ข้อมูลได้จากบันทึกเวชระเบียนในผู้ป่วยโรคหลอดเลือดสมองชนิดขาดเลือดเฉียบพลันที่มาถึงโรงพยาบาลในเวลา 4.5 ชั่วโมง และได้รับการรักษาด้วยยา rt-PA ตั้งแต่เดือนพฤษภาคม พ.ศ. 2551 ถึง เดือนเมษายน พ.ศ. 2555 โดยทำการประเมินเวลาและกระบวนการเข้าถึงโรงพยาบาล ระยะเวลาของขั้นตอนการรักษา และปัจจัยที่เกี่ยวข้องกับผลการรักษาที่ดีและไม่ดี

ผลการศึกษา: ในช่วงเวลาที่ทำการศึกษาพบว่ามีผู้ป่วยเข้าข่ายเข้าข่ายเกณฑ์ของการศึกษา 778 ราย ระยะเวลาเฉลี่ย onset to door 1.85±1.05 ชั่วโมง การไปโรงพยาบาลก่อนหน้าที่ไม่มียา rt-PA เป็นสาเหตุให้ผู้ป่วยมาถึงโรงพยาบาลล่าช้า (OR 1.62, *p*-value <0.001, 95% CI 1.28 ถึง 2.04) ค่าเฉลี่ย onset-to-needle time 3.08±1.11 ชั่วโมง ปัจจัยที่มีผลต่อผลการรักษาที่ไม่ดีได้แก่ การมีหัวใจเต้นผิดจังหวะแบบ atrial fibrillation (OR 2.38, *p*-value 0.003, 95% CI 1.33 ถึง 4.23) และเมื่อ onset-to-needle time มากกว่า 180 นาที (OR 14.78, *p*-value <0.001, 95% CI 7.91 ถึง 27.62)

สรุป: ผู้ป่วยที่มาโรงพยาบาลล่าช้ามีสาเหตุจากการไปโรงพยาบาลก่อนหน้าที่ไม่มียา rt-PA ภาวะการมีหัวใจเต้นผิดจังหวะแบบ atrial fibrillation และเมื่อ onset-to-needle time มากกว่า 180 นาที สัมพันธ์กับการผลการรักษาที่ไม่ดี