Original Article

Trend in Recombinant Tissue Plasminogen Activator (rtPA) Use for Ischemic Stroke in Thailand: Geographic Inequality, Cost of Treatment and Impact on 30-Day Case Fatality Rate

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Objective: To investigate trend of using thrombolysis in ischemic stroke patient under Universal Health Coverage Scheme from fiscal year 2011 to 2014 and explore cost of treatment and the effect of rtPA use on clinical outcome among patient who received and did not received rtPA.

Materials and Methods: The present analysis used 3 datasets comprised of the inpatient database of the Universal Health Coverage (UC) from the National Health Security Office, operating cost of hospitals from division of the Health Insurance, Ministry of Public Health and the Civil Registration Database from the Ministry of Interior. Patients with ischemic stroke in fiscal year 2011 to 2014 were retrieved based on the ICD10 code of I63. The 30-day case fatality was identified by using the date of death from the Civil Registration Database. Logistic regression was performed to compare 30-day case fatality between patient who received and did not receive rtPA with adjusted by sex, age, Charlson comorbidity index and year of admission.

Results: The rate of thrombolytic treatment has increased from 1.6% in 2011 to 3.8% in 2013. The percentage of rtPA treatment among male and female did not differ. The patients treated with rtPA were slight younger age, while Charlson comorbidity index did not differ. The geographical inequality of rtPA treatment gradually declined over time. Cost of treatment in rtPA usage was 4 times higher than without rtPA. The patients treated with rtPA had an increasing 30-day case fatality rate of 11% (OR 1.11, 95% CI 1.03-1.21) compared to those without rtPA after adjustment for other variables.Conclusion: The rate of using rtPA in universal health coverage scheme has been increasing during the study period but it remained low. More detail data collection is needed in the future to evaluate the benefit of rtPA use in Thailand.

Conclusion: The rate of using rtPA in the Universal Health Coverage Scheme has been increasing during the present study period but remained low. More detail data collection are needed in the future to evaluate the benefit of rtPA use in Thailand.

Keyword: Ischemic stroke, Thrombolysis rate, Recombinant tissue plasminogen activator, Cost of treatment

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Stroke is a common cause of death and a leading cause of disability in Thailand. In 2013, it was the leading cause of deaths among both females and males[(1)]. Thrombolytic therapy with recombinant tissue plasminogen activator (rtPA) has been recommended as standard treatment for acute ischemic stroke patients in many countries[(2,3)], mainly because it reduces the patient's disability[(4)]. Thailand has achieved the Universal Health Coverage (UHC) under the three main public health insurance schemes namely: Civil Servant Medical Benefit Scheme for about 10 million beneficiaries of civil servants and their dependents, Social Health Insurance Scheme for about 10 million private workers and Universal Health Coverage Scheme (UC Scheme) for the majority of Thai people about 47 million populations, 75% of total population. Due to data limitation, the present study mainly focuses on the UC Scheme only.

The utilization rate of thrombolysis for patients who had an ischemic stroke under the UC scheme was less than 0.1% during 2005 to 2007. Thus, the National Health Security Office (NHSO) encouraged their providers to establish a fast-track system to reduce the delay in accessing thrombolysis and explicitly included

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rtPA in the benefit package of the UC Scheme in 2008[5]. Extra reimbursement is given to the contracted hospital for providing rtPA, appropriate image technology and physical rehabilitation. Nevertheless, only 1.3% of all ischemic stroke patients in UC scheme were treated with rtPA in 2010[6]. Several countries reported that the rate of thrombolytic therapy was low during the first few years after thrombolytic agents were approved, but with significant increasing over time[7,8]. However, there were a few studies on the current situation of rtPA use in Thailand. The present study aimed to: 1) investigate the distribution of rtPA use over time, 2) estimate extra financial burden of rtPA use, and 3) explore the effect of rtPA use on clinical outcomes.

Materials and Methods

Databases from the three sources were used in the present study, namely: (1) the inpatient database of the UC Scheme which covered data of contracted public and private hospitals throughout the country, (2) operating cost of hospitals from division of Health Insurance, Ministry of Public Health (MOPH) Thailand, and (3) Civil Registration Database of Thailand from the Ministry of Interior (MOI), and variable available for analysis from each of these three data sources was shown in Figure 1.

Patients with ischemic stroke aged 18 years and over were retrieved of inpatient database from the National Health Security Office based on the International Classification of Disease coding I63. The first ever stroke cases newly admitted during fiscal year 2011 to 2014 were refined by excluding the patients who had previous history on ischemic stroke in 2010. Patients treated with thrombolysis were identified by ICD 9CM coding 9910. Demographic data, principle diagnosis, medical procedure and adjusted relative weight (AdjRw) of the selected cases were obtained.

Unit cost per AdjRw

The main source of data for calculation costs per AdjRw was the data set of the MOPH hospitals, fiscal year 2011 to 2014. In order to estimate the unit cost per AdjRw, the authors first computed the average unit cost per admission of each hospital using the quick method approach[9]. This method applied the cost weight or ratio between inpatient cost and outpatient cost from the most updated study[10] to disaggregate the admission cost from the overall operating cost. Then, the average admission cost was calculated according to the hospital levels which were district, general and regional hospital

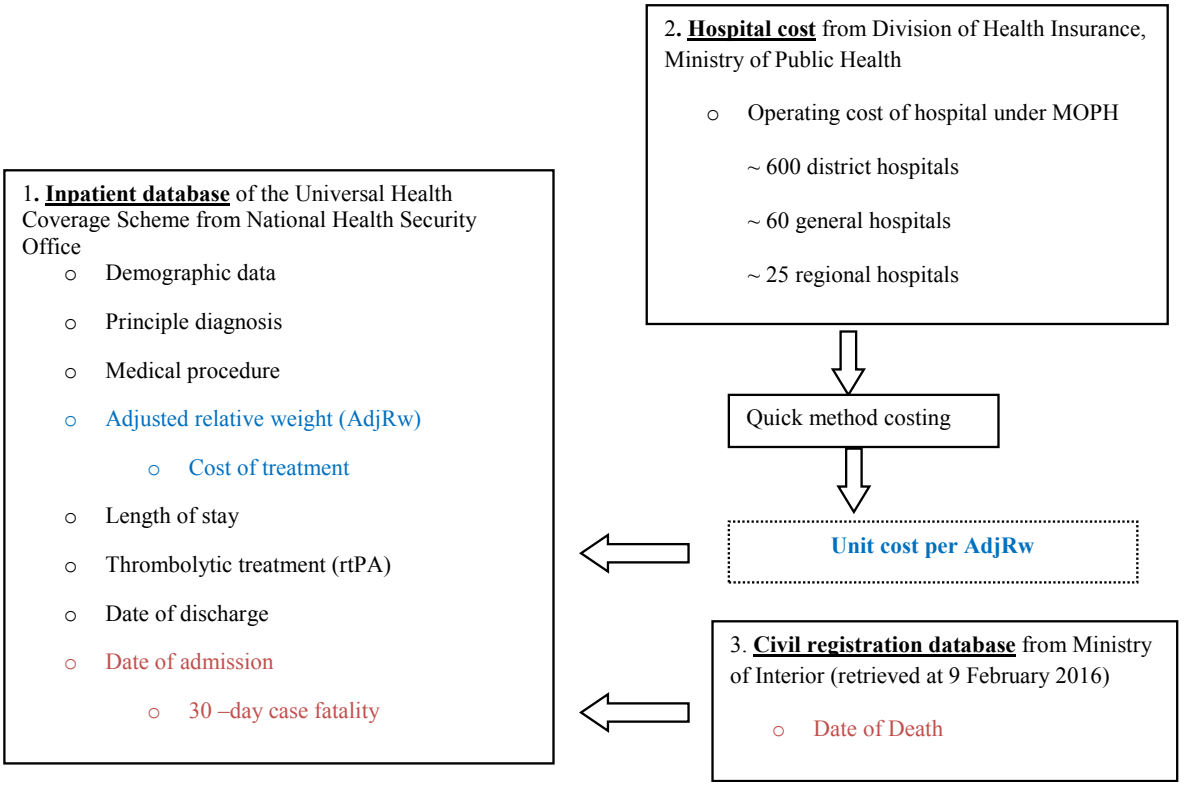

Figure 1 Framework and data sources

Table 1. Characteristic and outcomes of UHC patients with ischemic stroke (2011-2014)

	FY2011 n = 42,311	FY2012 n = 47,594	FY2013 n = 52,244	FY2014 n = 57,089
Rate of admission (1 per 100,000 UC beneficiary)	128.8	138.7	150.9	163.1
Males, n (%)	22,760 (53.8)	25,532 (53.7)	28,354 (54.3)	31,269 (54.8)
Age, mean (SD)	65.8 (13.3)	65.8 (13.2)	65.9 (13.1)	65.9 (13.1)
Charlson comorbidity index, n (%)				
• None (score=0)	22,279 (52.7)	25,027 (52.6)	26,572 (50.9)	28,995 (50.8)
• 1-2	16,268 (38.4)	18,501 (38.9)	20,980 (40.1)	22,971 (40.2)
• 3 and higher	3,764 (8.9)	4,066 (8.5)	4,692 (9.0)	5,123 (9.0)
Thrombolytic treatment, n (%)	662 (1.6)	1,007 (2.1)	1,559 (3.0)	2,156 (3.8)
30-day case fatality, n (%)	6,073 (14.4)	6,473 (13.6)	6,978 (13.4)	6,992 (12.3)

levels. The unit costs per AdjRw were estimated by dividing overall admission cost with AdjRw of each hospital level.

Cost of treatment between rtPA and non-rtPA receiver

The costs of treatment for each admission were allocated by multiplying the unit cost per AdjRw with the AdjRw from the inpatient database. An extra reimbursement was added to patients who were treated with thrombolytic therapy (60,600 baht in 2011 and 2012, respectively, and 49,000 baht in 2013 to 2014).

Charlson comorbidity index

Charlson comorbidity index was calculated based on the diagnosis of each patient. This index is commonly used for risk adjustment in administrative data set. It contains 17 comorbidity conditions including myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disorder, peptic ulcer, liver disease, diabetes, diabetes with complications, paraplegia, renal disease, cancer, severe liver disease, metastatic cancer and HIV. Each of these conditions is assigned weight score of 1, 2, 3 and 6 based on their potential influence on mortality[11]. The overall score reveals the cumulative increased likelihood of one-year mortality[12]. The higher score indicates the more severe of the burden of comorbidity.

Health outcomes

The 30-day case fatality was defined as the main health outcome. To identify patients who die within 30 days after admission, the date of death from the civil registration database was linked to the inpatient database using the 13-digit personal identification number.

Statistical analysis

For descriptive statistics, percentages for categorical data and means and standard deviations for continuous data were calculated. Cost of treatment during 1st year was reported in median and interquartile range (IQR). Multiple Logistic regression was used to compare 30-day case fatality rate between rtPA and non-rtPA treatment adjusting by sex, age, Charlson comorbidity index and fiscal year. All analyze were performed using R version 3.0.0.

Results

General trend

Table 1 showed the rate of admissions of ischemic stroke in UC beneficiary shifted from 128.8 to 163.1 per 100,000 populations in fiscal year 2011 and 2014, an increase of 8.9% per year. Patient's characteristics barely changed proportion of gender, age and Charlson comorbidity index. The majority group was male with age average about 66 year. Charlson comorbidity index presented that around half of them had no severe comorbidity. Thrombolytic treatment regularly increased in term of cases (662 cases in 2010 to 2,156 cases in 2014), and percentage (1.6% to 3.8% in 4 years). Conversely 30-day case fatality rate steadily declined from 14.4 to 13.3 in 4 years.

Table 2 compared the background characteristics among patients treated with thrombolysis and those not treated with thrombolysis between 2011 and 2014. The percentage of patients receiving rtPA among males and females did not differ indicating no gender disparity in access to this treatment. The treated group had slightly younger age while Charlson comorbidity index did not differ.

Geographic distribution

Figure 2 presented the geographical variation

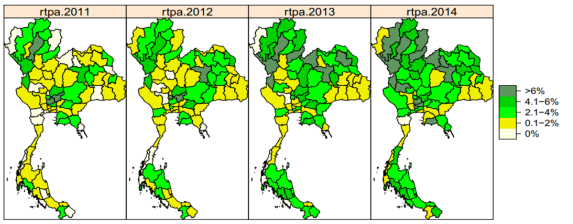

Figure 2 Geographical distribution of rtPA treatment of UC Scheme patients during 2011-2014

in the percentage of patients receiving treatment with rtPA during 2011-2014 across the country. The geographical inequality of rtPA treatment gradually decreased during the 4-years period, while overall rtPA treatment regularly increased. By the end of the study period, UC patient in each province had been exposed to rtPA treatment.

Table 3 compared health outcome of ischemic stroke between patients treated with rtPA and those who were not. The rate of intracerebral hemorrhage among those received rtPA was 10 times higher than those who did not receive rtPA. The 30-day case fatality rate among those received rtPA was slightly lower than patients who did not receive rtPA in each year except in 2013.

Cost of treatment

Table 4 compared overall costs during the first year of treatment between the two groups. The flat rate for rtPA reimbursement for each year (right most column) decreased from 60,600 baht in 2011 and 2012 to 49,000 baht in 2013 and 2014, due to declining price of rtPA drug. In addition to the direct reimbursement of rtPA, patients with rtPA consumed consistently higher cost than non-rtPA recipients. Overall cost of treatment with rtPA was 4 times higher than treatment without rtPA. The higher cost of rtPA treatment was due to the higher average relative weight of diagnosis related group, (Table 5).

Effect on mortality

Table 6 showed crude and adjusted odds ratios of various risk factors on 30-day case fatality rate. Patients treated with rtPA had an 11% higher case fatality rate compared to those treated without rtPA after adjustment for other variables. The mortality risk reduced over the years with significant linear trend. Males had a lower risk than female and the risk increased with increasing age in a linear fashion.

Discussion

The rate of thrombolytic treatment in patient with ischemic stroke increased over the 4-year period. This trend had neither a specific geographic pattern nor disparity between genders. Use of rtPA increased the total costs per case due to the flat rate of reimbursement set by the NHSO and other reimbursement items, both were higher than the reimbursement without rtPA use. While the 30-day case fatality rate of ischemic stroke patients was declining, the rate among those treated with rtPA was average 11% higher than those treated without rtPA after adjustment for sex, age, Charlson's comorbidity index and year of admission.

There may be various reasons for the increasing trends in ischemic stroke admissions. The age distribution of these patients remained constant during the study period. Thus demographic transition could not be a reason for the increase. An increase of 7% - 8% in the number of cases was also too high to be explained by epidemiological transition. Improvement of access to care may not be a good explanation either because

Table 2. Trend distribution among patients with ischemic stroke who were treated with rtPA and those who were not (2011-2014)

	FY2011		FY2012		FY2013		FY2014	
	Non-rtPA (n=41,649)	rtPA (n=662)	Non-rtPA (n=46,587)	rtPA (n=1,007)	Non-rtPA (n=50,685)	rtPA (n=1,559)	Non-rtPA (n=54,933)	rtPA (n=2,156)
Sex								
Male, n (%)	22,404 (98.4)	356 (1.6)	24,974 (97.8)	558 (2.2)	27,495 (97.0)	859 (3.0)	30,102 (96.3)	1,167 (3.7)
Female, n (%)	19,245 (98.4)	306 (1.6)	21,613 (98.0)	449 (2.0)	23,190 (97.1)	700 (2.9)	24,831 (96.2)	989 (3.8)
Age, mean (SD)	63.8 (12.1)	65.8 (13.3)	63.0 (12.7)	65.8 (13.1)	62.8 (12.7)	65.9 (13.1)	63.2 (12.9)	65.9 (13.1)
Charlson comorbidity index, mean (SD)	0.8 (1.0)	0.8 (1.1)	0.8 (1.1)	0.8 (1.1)	0.8 (1.0)	0.8 (1.1)	0.8 (1.1)	0.8 (1.1)

Table 3. Comparison of health outcome among rtPA receipts and non-rtPA receipts

	FY2011		FY2012		FY2013		FY2014	
	Non-rtPA (n=41,649)	rtPA (n=662)	Non-rtPA (n=46,587)	rtPA (n=1,007)	Non-rtPA (n=50,685)	rtPA (n=1,559)	Non-rtPA (n=54,933)	rtPA (n=2,156)
Intracerebral hemorrhage, n (%)	145 (0.3)	15 (2.3)	182 (0.4)	40 (4.0)	200 (0.4)	71 (4.6)	202 (0.4)	103 (4.8)
30-day case fatality, n (%)	5,985 (14.4)	88 (13.3)	6,341 (13.6)	132 (13.1)	6,753 (13.3)	225 (14.4)	6,729 (12.3)	263 (12.2)

Table 4. Comparison of costs between non rtPA and rtPA groups at the first year of treatment

Fiscal Year	Cost of Non-rtPA treatment (median, IQR)	Cost of rtPA treatment	
		Other reimbursement (median, IQR)	Direct rtPA reimbursement (median, IQR)
2011	20,898 (13,568, 35,723)	28,915 (14,456, 50,063)	60,600
2012	17,251 (14,087, 30,479)	28,034 (14,092, 40,323)	60,600
2013	16,443 (13,029, 28,181)	18,732 (14,075, 30,442)	49,000
2014	15,739 (11,826, 25,578)	20,796 (11,826, 35,642)	49,000

Table 5. Comparison of relative weight of diagnosis related group (adjRw of DRG) for non rtPA and rtPA groups

	Average AdjRw	
Fiscal year	Non-rtPA (mean, SD)	rtPA (mean, SD)
2011	2.5 (3.4)	2.8 (6.1)
2012	2.3 (3.3)	3.0 (4.1)
2013	2.1 (2.9)	2.7 (3.5)
2014	2.0 (2.6)	2.7 (3.8)

the Universal Health Coverage had been in use for more than one decade. A more likely reason was improved image technology and personal diagnostic procedures for stroke may enable more definite diagnose of ischemic stroke.

The rate of thrombolysis treatment in UCS has been regularly increased over time after NHSO started the vertical program for acute ischemic stroke in 2009. However, the use rate of 3% - 4% was very low compared to the optimal rate. It is estimated that without time delay approximately 24% of ischemic stroke patients would be treated with rtPA[13]. The steady rising in rate of rtPA utilization may relate to 2 main factors. First, there is no financial constraint for UC beneficiaries. Financial barrier is one of the main reasons for low thrombolytic rates in developing countries due to the high cost of thrombolytic drug[14]. NHSO started top-up policy for rtPA treatment where providers were reimbursed for the thrombolysis agents and also covers other expensive services such as CT scan and rehabilitation. However, the effectiveness of this policy might need some lapsed time to be effective. Hospitals needed time to improve facilities and human resources. Second, the improvement of referral system was reported in several hospital-base studies. Integrating an acute stroke referral network in a community-based setting reduced both door to needle time and onset to treatment time[15]. Consequence, the eligible patients had more opportunity in receiving rtPA in time.

High cost of thrombolytic treatment has been reported in many studies[16, 17]. The present study, the cost of treatment with rtPA was much higher than treatment without rtPA. These results reflected the high price at the early year of the policy.

The positive association between rtPA use and mortality was against one's expectation. This finding concurs with those from a recent systematic review that thrombolysis increased early mortality[18]. Patients treated with rtPA have a higher risk of symptomatic intracerebral hemorrhage, increased the risk of death during the acute phase. There were no differences in long term death (3 - 6 months) between patients treated with rtPA or without rtPA[19]. Several potential confounding variables, such as high blood pressure, hyperglycemia, and stroke severity, were not included in the analysis. These factors are known to have a strong association with mortality[20-22]. Thrombolysis clearly improves neurological recovery and reduces the incidence of disability[4,19,22]. Nevertheless, the present study cannot explore these benefits since NHSO database did not contain the stroke severity level at pre- and post-admission. Measuring the stroke

Table 6. Determinants of 30-day case fatality due to ischemic stroke

Variable	Crude OR (95% CI)	Adjusted OR (95% CI)	*P*-value[a]
Male	0.73 (0.71-0.75)	0.83 (0.81,0.85)	<0.001
Age group (ref:18-34 year)			
35-44	1.16 (0.99,1.36)	1.14 (0.97,1.33)	<0.001[b]
45-54	1.05 (0.91,1.22)	1.03 (0.88,1.19)	
55-64	1.26 (1.09,1.46)	1.21 (1.05,1.40)	
65-74	1.80 (1.56,2.08)	1.71 (1.48,1.97)	
75-84	2.89 (2.51,3.34)	2.75 (2.38,3.17)	
85 year and over	4.84 (4.18,5.60)	4.65 (4.02,5.39)	
Charlson comorbidity index (ref:0)			
1-2	1.39 (1.35,1.43)	1.4 (1.37,1.44)	<0.001
3 and higher	1.96 (1.88,2.04)	2.01 (1.92,2.1)	
Fiscal year (ref:2011)			
2012	0.94 (0.90,0.98)	0.94 (0.91,0.98)	<0.001[b]
2013	0.92 (0.89,0.95)	0.91 (0.88,0.95)	
2014	0.83 (0.80,0.86)	0.83 (0.80,0.86)	
Thrombolytic treatment	0.99 (0.91,1.07)	1.11 (1.03,1.21)	0.009

[a] Likelihood ratio test

[b] Test for linear trend

severity is recommended in the clinical guideline and followed in every hospital. Thus combining this kind of information to NHSO database is useful for further study.

The authors' findings had limitations that should be considered. Main limitation was lack of disability information in the outcome, which rtPA is supposed to prevent. The information on history of previous stroke was also retrieved from admission records in the NHSO database one year back, not directly from clinical history tracking. The findings thus should be interpreted with caution.

Conclusion

While the rate of rtPA use has increased, lack of available data failed to show it benefit. More detailed data collection is needed in the future to evaluate the effectiveness of rtPA use in Thailand.

What is already known on this topic?

Recombinant tissue plasminogen activator (rtPA) was proven to reduce disability in acute ischemic stroke patient. However, time limitation is a major barrier to access rtPA because this therapy must be administered within 4.5 hours after stroke onset. The NHSO encouraged their providers to establish a fast-track system to reduce the delays in accessing thrombolysis, the low utilization rates of rtPA treatment for ischemic stroke in UC patient were observed at the beginning year.

What this study adds?

The rate of thrombolysis use in the UCS has been regularly increased over time from year 2011 to 2014. This rising trend had neither geographic and gender inequality. However, there was increased mortality rate among rtPA used and 30-day fatality.

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Potential conflicts of interest

The authors declare no conflict of interest.

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