Original Article

Rate of Intravenous Thrombolysis with Recombinant Tissue Plasminogen Activator in Thai Universal Health Coverage Scheme Patients

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Background: Stroke is a major and increasing health burden worldwide. Intravenous thrombolysis with recombinant tissue plasminogen activator (rt-RA) has proved to be a highly effective therapy for minimizing stroke morbidity and mortality, but given the 4.5 hours optimum treatment window, achieving high rate of rt-PA administration is still a challenging issue.

Objective: The present study aimed to investigate trends in intravenous thrombolysis with recombinant tissue plasminogen activator rates in each Health Area and province in Thailand.

Materials and Methods: The present study used a descriptive retrospective survey design. It used data from Thailand's National Health Security Office for Universal Health Coverage Scheme patients, 15 years and over with cerebral infarction from budget year 2009 to 2020 (until July, 31st).

Results: The overall rate of rt-PA administration in Thailand increased from 0.18% (57 cases from total 32,421 cases) in 2009 to 7.95% (5,863 cases from total 73,769 cases) in 2020 (until July, 31st). Health Area 11 had the highest rate of rt-PA administration (10.82%, 559 out of 5,165 cases), with Health Area 9 having the lowest rate (6.19%, 548 out of 8,849 cases).

Conclusion: From 2009 to 2020, rate of the rt-PA treatment in Thai Universal Health Coverage Scheme patients, 15 years and over, steadily increased. In order to achieve higher rates of rt-PA treatment, further studies are needed to address the barriers of rt-PA treatment for further systematic development of acute stroke care.

Keywords: Recombinant tissue plasminogen activator; Treatment rate; Acute stroke; Cerebral infarction

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Stroke is an increasing major global health burden, and a leading cause of mortality and morbidity in both developing and developed countries. It is associated with risk factors such as hypertension, diabetes mellitus, dyslipidemia, and smoking[1], and has serious socioeconomic impacts on patients and caregivers.

Thailand's stroke, prevalence in 2014 was 1.88% among adults 45 years and older[2].

Cost of stroke treatment is determined by patient characteristics, pathology, treatments, and phases of care. In 2012, the average stroke admission cost in Thailand was 32,372 Baht. Average cost of acute phase (from admission date to referral date to rehabilitation service) was higher than sub-acute phase (functional restoration), 51,031 and 19,256 Baht, respectively[3].

Intravenous thrombolysis with recombinant tissue plasminogen activator (rt-RA) has proved to be a highly effective therapy in minimizing long term disability, neurological impairment, and stroke-related mortality[4-7]. Thai clinical practice guidelines for ischemic stroke intervention recommend thrombolytic administration for eligible ischemic stroke patients (Class I; Level of Evidence A)[8]. Because of the 4.5 hours critical treatment period, rt-PA administration has underperformed, and achieving high rate of rt-PA administration is still a challenging issue. The adequacy of patients' awareness of complex symptoms, varying accessibility to healthcare services (especially in rural areas), the availability of CT scan, rt-PA, and expertise may all impact on treatment rates.

The present study aimed to present the rate of intravenous thrombolysis intervention with recombinant tissue plasminogen activator by Health Areas and provinces in Thailand. Such analyses would be beneficial for systematic development of acute stroke care policies and practice in the Thai Health Services.

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Materials and Methods

Study design

The present study was a retrospective survey of

all Thai patients under the Universal Health Coverage (UHC) scheme, 15 years and over, who suffered a cerebral infarction from budget year 2009, to July 31st 2020 registered in National Health Security Office (NHSO).

Operational definitions

Acute ischemic stroke was defined as a sudden onset of focal neurological deficit lasting more than 24 hours with evidence of cerebral infarction on CT scan or a normal CT scan without evidence of intracranial hemorrhage.

Health Areas were defined as a group of adjacent provinces arranged by the Thai Ministry of Public Health (MOPH) to provide medical services for local citizens and develop transferal system among primary, secondary, and tertiary health care centers within that region. Each of these 13 Health Areas is responsible for about 3 to 6 million people living in their respective provinces.

Health Area 1 consists of Chiang Mai, Chiang Rai, Phrae, Nan, Phayao, Lampang, Lamphun, and Mae Hong Son.

Health Area 2 consists of Tak, Phetchabun, Phitsanulok, Uttaradit, and Sukhothai.

Health Area 3 consists of Kamphaengphet, Phichit, Nakhon Sawan, Chai Nat, and Uthaithani.

Health Area 4 consists of Saraburi, Nonthaburi, Lopburi, Angthong, Nakhon Nayok, Singburi, Phra Nakhon Si Ayutthaya, and Pathumthani.

Health Area 5 consists of Phetchaburi, Samut Sakhon, Samut Songkhram, Prachuap Khiri Khan, Suphanburi, Nakhon Pathom, Ratchaburi, and Kanchanaburi.

Health Area 6 consists of Sa Kaeo, Prachinburi, Chachoengsao, Samut Prakan, Chonburi, Chanthaburi, Rayong, and Trat.

Health Area 7 consists of Kalasin, Khon Kaen, Maha Sarakham, and Roi Et.

Health Area 8 consists of Udonthani, Sakon Nakhon, Nakhon Phanom, Loei, Nong Khai, Nong Bua Lamphu, and Bueng Kan.

Health Area 9 consists of Chaiyaphum, Nakhon Ratchasima, Buriram, and Surin.

Health Area 10 consists of Ubon Ratchathani, Sisaket, Mukdahan, Amnat Charoen, and Yasothon.

Health Area 11 consists of Nakhon Si Thammarat, Suratthani, Phuket, Krabi, Phang Nga, Ranong, and Chumphon.

Health Area 12 consists of Songkhla, Satun, Trang, Phatthalung, Pattani, Yala, and Narathiwat.

Health Area 13 consists of Bangkok.

A Budget year runs from October, 1st to September, 30th of the following year.

Statistical analysis

Data from all National Health Security Office (NHSO) patients who met inclusion criteria were entered into Microsoft Excel 2016. Descriptive data were presented by frequency, percentages, and in graphical form.

Ethical review

The research protocol was reviewed and approved by the Committee for Human Ethics Research, Khon Kaen University (HE631574).

Results

Overall rate of rt-PA administration in Thailand increased from 0.18% (57 cases from total 32,421 cases) in 2009 to 7.95% (5,863 cases from total 73,769 cases) until July, 31st 2020 (Figure 1). Total cerebral infarction patients also increased each year as shown in Figure 2.

In 2020 (until July, 31st), Health Area 11 (Suratthani, Nakhon Si Thammarat, Krabi, Phang Nga, Phuket, Ranong, Chumphon) had the highest rate of rt-PA administration of 10.82% (559 out of 5,165 cases), whereas Health Area 9 (Nakhon Ratchasima, Buriram, Surin, Chaiyaphum) had the lowest rate at 6.19% (548 out of 8,849 cases).

Trends in the rate of rt-PA administration for Health Areas 1 to 13 from 2009 to 2020 are shown in Figure 4 and Figure 5.

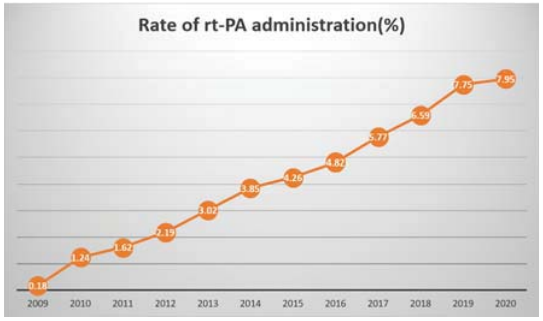

Figure 1. Rate of rt-PA administration for Thai UHC patients from budget year 2009 to July, 31st 2020.

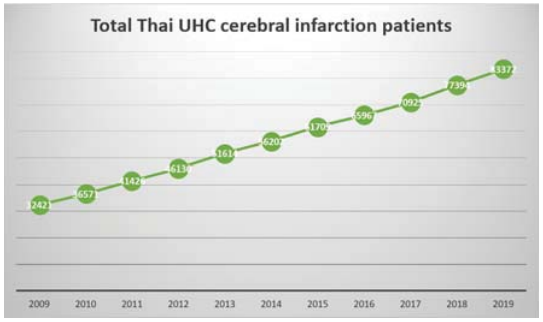

Figure 2. Total Thai UHC cerebral infarction patients from budget year 2009 to 2019.

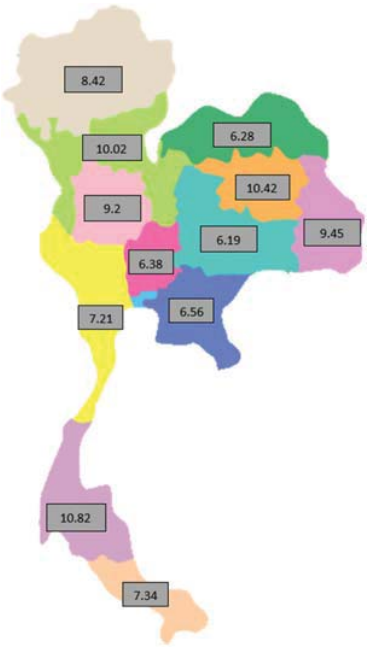

Figure. 3 Demonstrates the rt-PA administration rate for each Health Areas in 2020 (until July, 31st) (%).

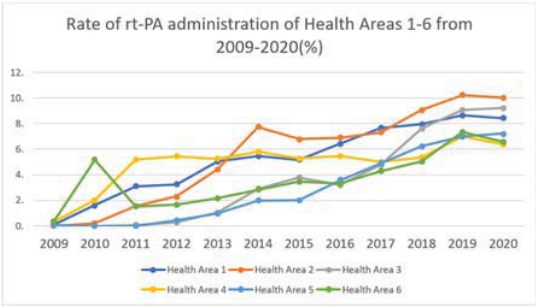

Figure. 4 Rate of rt-PA administration of Health Areas 1 to 6 from 2009 to 2020.

Figure 6 to 18 demonstrate the rate trends of rt-PA administration for province in each Health Area from 2009 to 2020 (%).

The 3 provinces with the highest rate of rt-PA administration in 2020 (until July, 31st) were Mukdahan (26.79%), Suratthani (20.75%), and Tak (16.64%). In Mukdahan, among 7 districts, Muang Mukdahan was the only district that could provide rt-PA treatment (27.47%, 86 cases out of 313 cases). In Suratthani, the 4 districts that could provide rt-PA treatment were Muang Suratthani

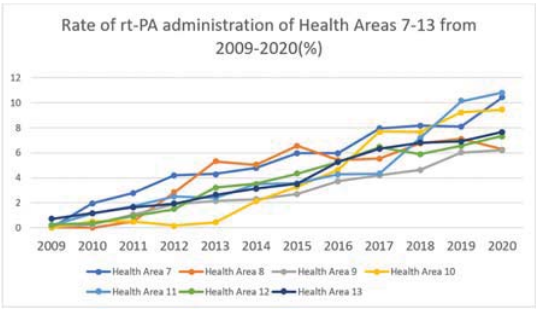

Figure 5. Rate of rt-PA administration of Health Areas 7 to 13 from 2009 to 2020.

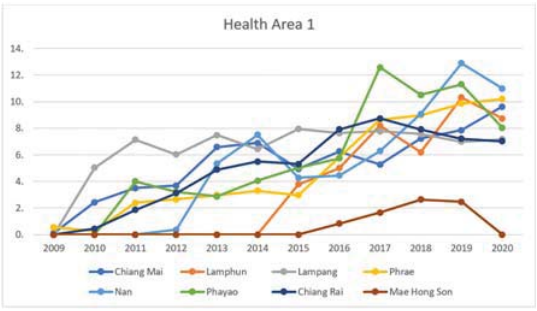

Figure 6. Rate of rt-PA administration of Health Areas 1 from 2009 to 2020.

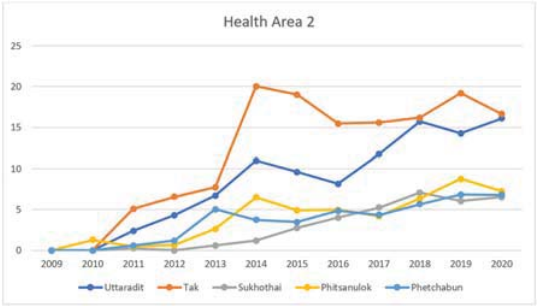

Figure 7. Rate of rt-PA administration of Health Areas 2 from 2009 to 2020.

(28.19%, 181 cases out of 642 cases), Koh Samui (14.42%, 15 cases out of 104 cases), Kanchanadit (23.68%, 36 cases out of 152 cases), Wiang Sa (12.5%, 11 cases out of 88 cases). The 2 Tak districts that could provide rt-PA treatment were Muang Tak (19.36%, 67 cases out of 346 cases) and Mae Sot (15.26%, 29 cases out of 190 cases).

The 3 provinces with the lowest rate of rt-PA administration in 2020 (until July, 31st) were Mae Hong Son

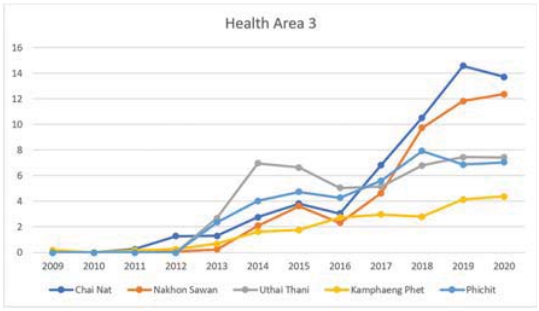

Figure 8. Rate of rt-PA administration of Health Areas 3 from 2009 to 2020.

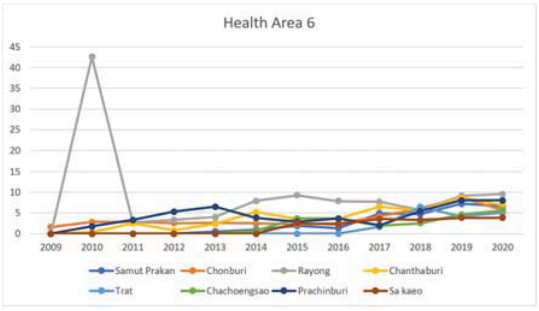

Figure 11. Rate of rt-PA administration of Health Areas 6 from 2009 to 2020.

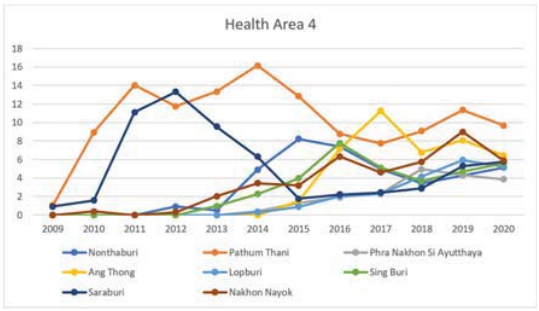

Figure 9. Rate of rt-PA administration of Health Areas 4 from 2009 to 2020.

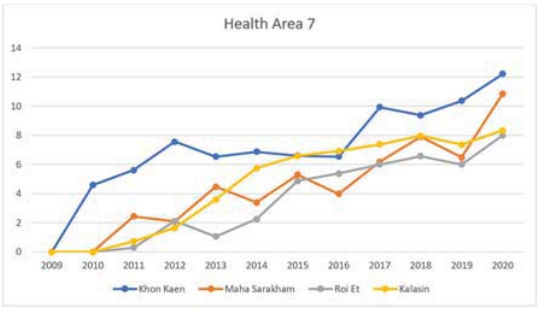

Figure 12. Rate of rt-PA administration of Health Areas 7 from 2009 to 2020.

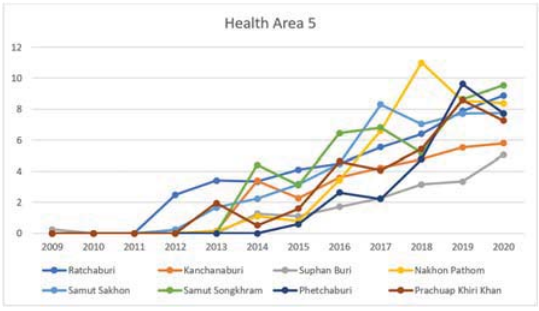

Figure 10. Rate of rt-PA administration of Health Areas 5 from 2009 to 2020.

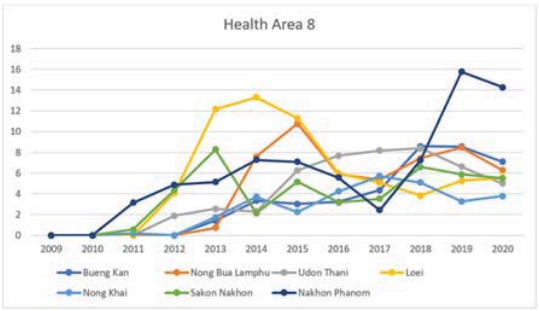

Figure 13. Rate of rt-PA administration of Health Areas 8 from 2009 to 2020.

(0%), Patthalung (2.49%), and Yasothon (3.57%). No cerebral infarction patients received rt-PA treatment in Mae Hong Son province during this period, while in 2019, Muang Mae Hong Son district (Srisungwan Hospital) provided rt-PA treatment for 5.17% of their cases (3 cases out of 58 cases). Muang Patthalung district was the only district that could provide rt-PA treatment with the rate of 2.53% (17 cases out of 672 cases). In Yasothon, only Muang Yasothon district could provide rt-PA treatment and did so for 3.76% of cases (26 cases out of 691 cases).

Discussion

overall rate of rt-PA administration in Thailand in the Universal Health Coverage Scheme has increased

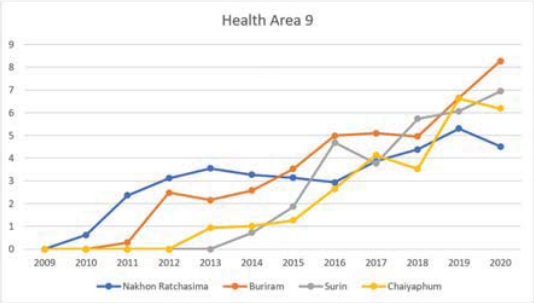

Figure 14. Rate of rt-PA administration of Health Areas 9 from 2009 to 2020.

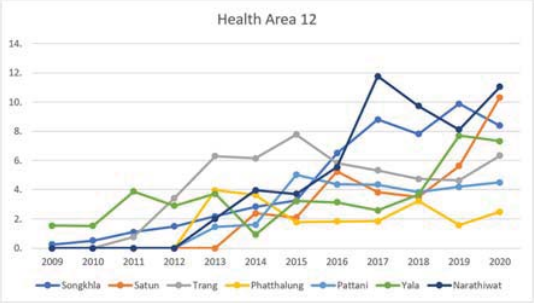

Figure 17. Rate of rt-PA administration of Health Areas 12 from 2009 to 2020.

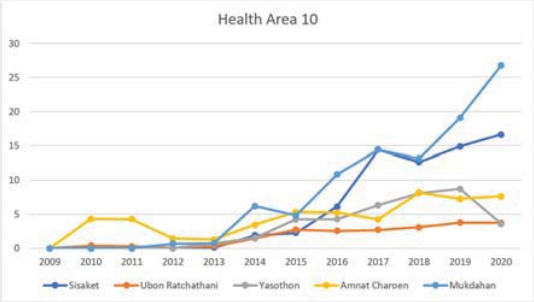

Figure 15. Rate of rt-PA administration of Health Areas 10 from 2009 to 2020.

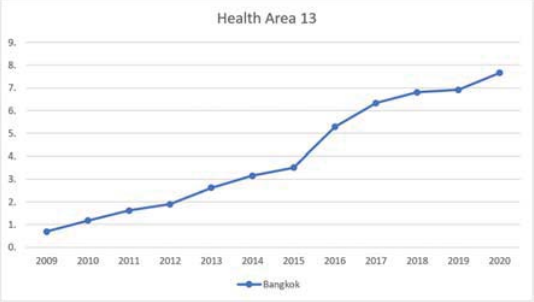

Figure 18. Rate of rt-PA administration of Health Areas 13 from 2009 to 2020.

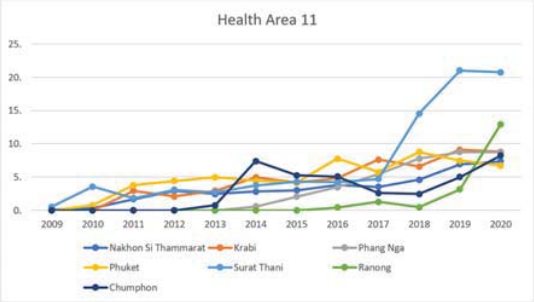

Figure 16. Rate of rt-PA administration of Health Areas 11 from 2009 to 2020.

annually since 2009. From previous studies[9-17], the barriers to thrombolysis therapy include inadequate patients' knowledge about stroke symptom acuity, travel time to treatment, attending at a non-stroke treatment center, staff expertise, facilities and staffing levels, and other infrastructure elements. Our finding of increased rate of rt-PA intervention correlates with increased rt-PA and CT scan availability, improved physician training and skills, improved community health education, and increased access to hospitals in Thailand.

In our study, Mukdahan had the highest rate of rt-PA administration in 2020 (until July, 31st). This could be related to shorter travel duration, as Mukdahan is in a plains area with shorter travel times to hospital than mountainous areas. Mae Hong Son, with the lowest rt-PA administration, is in a mountain-landscape area with longer travel times to hospital. Patients are more likely to arrive at the emergency room more than 4.5 hours after stroke onset and therefore not be administered rt-PA treatment.

The role of stroke units in acute ischemic stroke care is firmly established[18,19], but in limited resource countries, including Thailand, the small number of stroke units is a challenge for achieving higher rates of rt-PA treatment. Thus, low rt-PA treatment rates may be the consequence of the complexity in establishing specialized stroke units as referred to Irene L. Katzan, et al[20] and Michael D. Hill, et al[21].

Several studies have demonstrated safety of thrombolysis administration in departments other than stroke units. Dittrich, et al[22] compared 12,232 patients admitted to departments of neurology, internal and geriatric

Table 1. Demonstrate the rate of rt-PA administration for Health Areas 1 to 13 from 2009 to 2020 (%).

Year/ Health area	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
1	0.09	1.61	3.08	3.24	5.04	5.47	5.15	6.41	7.65	7.95	8.66	8.42
2	0.00	0.21	1.54	2.31	4.41	7.73	6.79	6.88	7.31	9.06	10.22	10.02
3	0.05	0.00	0.07	0.30	1.05	2.91	3.78	3.19	4.78	7.61	9.05	9.20
4	0.34	2.00	5.19	5.44	5.23	5.82	5.26	5.46	5.00	5.36	7.01	6.38
5	0.04	0.00	0.00	0.43	0.98	1.97	2.01	3.56	4.87	6.21	7.01	7.21
6	0.36	5.17	1.51	1.65	2.15	2.83	3.47	3.30	4.29	5.04	7.34	6.56
7	0.00	1.94	2.77	4.18	4.30	4.79	5.98	5.98	7.94	8.17	8.08	10.42
8	0.00	0.00	0.49	2.82	5.30	5.04	6.55	5.41	5.55	6.75	7.13	6.28
9	0.00	0.25	1.04	1.86	2.14	2.27	2.71	3.73	4.21	4.64	6.02	6.19
10	0.00	0.49	0.50	0.17	0.41	2.12	3.29	4.64	7.69	7.67	9.22	9.45
11	0.19	1.13	1.70	2.49	2.40	3.50	3.55	4.27	4.31	7.19	10.12	10.82
12	0.25	0.35	0.95	1.50	3.20	3.51	4.33	5.25	6.44	5.89	6.55	7.34
13	0.69	1.17	1.62	1.90	2.62	3.15	3.51	5.28	6.33	6.80	6.91	7.66

medicine in 42 hospitals in Germany. Results showed that patients admitted to neurology departments' stroke units underwent more diagnostic procedures compared with other departments, but also found that thrombolysis could be safely administered in hospitals without specialized stroke units. Michael Bergman, et al[23] showed that rt-PA treatment carried out in a specially-organized unit within the department of internal medicine could serve as an effective alternative for hospitals without stroke units. This would increase the administration of thrombolytic therapy within the critical treatment period. These studies suggest if we ensure rural hospitals, without dedicated stroke units, have the potential to administer rt-PA and provide efficient acute stroke care, rt-PA treatment rate will be increased. Several models and protocols have been developed to increase rate of rt-PA treatments. Telemedicine methods have been developed to support the institution of stroke units, and several trials had demonstrated the reliability of neurological assessments via teleconference[24-28].

In Thailand, the I-San Stroke Network[29] has been developed for Health Area 7. Their missions are to promote stroke health care system development, to establish strong health teams, and improve community health education in every aspect including stroke presentation, treatment, Stroke Fast Track system, primary and secondary prevention, long term care and rehabilitation. Strengthening community hospitals by enabling them to administer thrombolytic drugs for acute ischemic stroke will decrease transport to treatment time and increase patients' opportunities to receive rt-PA. Since the advent of the I-San Stroke network, the rt-PA administration rate in Health Area 7 in the Universal Health Coverage Scheme has increased and is now above the average rate for all Health Areas. The Stroke Network of Maharaj Nakorn Chiang Mai Hospital[30], a hub and node model, has also been successful at increasing rt-PA administration rate.

Conclusion

From 2009 to July 2020, the rate of the intravenous thrombolysis with recombinant tissue plasminogen activator for Thai UHC stroke patients, 15 years and older, increased from 0.18% to 7.95% between 2009 and 2020. However, patient's awareness of stroke symptoms, reduced transport time to the hospital with CT scan and rt-PA treatment availability, and emergency department staff expertise remain goals for further improving treatment rates.

What is already known on this topic?

Treatment of acute ischemic stroke patients with thrombolytic drug is the standard treatment. But, in the past the patients receiving the treatment still had low rates of thrombolytic treatment.

What this study adds?

At present, Thailand has a treatment system that provides thrombolytic treatment in all provinces. And in large community hospitals This resulted in an approximate 8%.

Acknowledgements

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Potential conflicts of interest

The authors declare no conflict of interest.

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