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Rehospitalization within 30 days after Thrombolytic Therapy among Acute Ischemic Stroke Patients

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Abstract: Stroke patients not only have longer lengths of stay, but also higher rehospitalized (RH) rates. Moreover, after the beginning of the thrombolytic therapy era in Thailand, there are limited data about this condition. The objective of this study was to evaluate frequency and contributing factors for 30-day unplanned RH in acute ischemic stroke (AIS) patients treated with thrombolytic agent in Maharat Nakhon Ratchasima Hospital (MNRH). It was conducted as a cohort study in the patients with AIS and treated with thrombolytic agent in MNRH between January 2011 and December 2014, The RH was documented as the patients who were unplannedly admitted within 30 days after discharged from the initial-admission. The details on initial-admission and RH were collected and compared between RH and non-RH patients for identifying the factors associated with unplanned RH. A total of 238 patients with 128 males (53.8%) were enrolled in this study. The 30-day RH occurred in 24 patients (10.1%) and about 80% presented within 15 days after discharged. The common causes of 30-day RH were pneumonia (41.6%), recurrent stroke (16.6%) and cardiovascular event (16.6%). The patients who developed pneumonia and intracerebral hemorrhage during initial admission were strongly associated with RH, with relative risk = 4.75 (2.31-9.76) and 3.47 (1.63-7.39), respectively. In conclusions, the rate of 30-day RH in AIS patients with thrombolytic therapy in MNRH was 10.1% (95%CI 6.3-13.9%) and about 80% of this event occurred within the first 15 days after discharge. Pneumonia (41.6%) was the most common causes of RH. The significantly associated factors for 30-day RH were pneumonia or intracerebral hemorrhage after thrombolytic treatment.

Key words: **rehospitalization, acute ischemic stroke, thrombolytic therapy**

Introduction

Stroke is a major public health problem worldwide. In Thailand, the estimated prevalence of stroke is 1.9% among adults 45 years and older[1]. Stroke patients not only have longer lengths of stay, but also higher rehospitalized rates.

The RH of disable stroke patients is common. The rate of rehospitalization (RH) within 1-year after

stroke is ranging from 20.0-60.0%; and approximately 25.0% of all RHs occurred within 1 month after initial event (about 6.0-21.0% from the previous studies)[2-6]. These estimations vary among countries, level of healthcare system, socioeconomic status and treatment during initial-admission. In Thailand, the study from Songklanagarind Hospital found 8.0% of stroke patients were rehospitalized within 16 weeks after discharged[7].

In the present day, thrombolytic therapy in selected ischemic stroke patients has documented better outcome more than conventional therapy[8]. In Thailand, However, there are limited data on the incidence, causes and outcomes of RH in post-stroke patients after the beginning of thrombolytic therapy.

Maharat Nakhon Ratchasima Hospital (MNRH) is a tertiary care hospital in North-Eastern region of Thailand. In Department of Medicine, over 20,000 patients are admitted each year. This number included 5.0% of 30-day RH, of which acute ischemic stroke (AIS) is one of the leading causes. Therefore, clear understanding of RH is essential to improve the care and reduce the RH rate in the patients.

The objective of this study were to evaluate the frequency of 30-day of unplanned RH and to determine the factors contributing to RH in acute AIS patients treated with intravenous recombinant tissue plasminogen activator (IV-rtPA).

Methods

This research was a prospective cohort study. Patients with stroke were recruited bases on the following inclusion criteria: (1) admitted and discharged in MNRH during January 2011 and December 2014 (which next refer as initial-admission), (2) the principle diagnosis was AIS, and (3) treated with IV-rtPA. The patients that died during initial-admission and the patients who lost to follow up before 30 days were excluded from the study. From sample size calculation using infinite population proportion formula, at least of 186 patients were required to obtain significant outcomes with a 95% confidence interval (95%CI) and 5% of allowable error.

Rehospitalization was documented as the patients who were unplanned admission within 30 days after discharged from initial-admission. The planned admissions for elective procedure as, elective surgery, rehabilitation, radiation therapy or dialysis were not considered as RH in the study.

After patients were enrolled into the study, data were collected from initial admission including baseline characteristics, types of infarction (according to TOAST classification)[9], cardiovascular (CV) risk factors (hypertension, diabetes and dyslipidemia), presence of atrial fibrillation (AF), in-hospital complications (pneumonia, intra-cerebral hemorrhage - ICH, infections), severity of stroke based on the National Institute of Health Stroke Scale - NIHSS[8], Glasgow coma score - GCS and modified Rankin scales - MRS[10], discharge status (home discharge or discharge by refer). In patients who were rehospitalized, the details about RH such as, causes, duration of discharge from initial-admission, length of hospital stay and outcomes were recorded. The data between RH and non-RH patients were examined for identifying the incidence, causes and associated factors of unplanned RH according to study objectives.

The data were analyzed using mean and standard deviation or median, minimum, maximum and interquartile range, as appropriate. The categorical data

were analyzed for frequencies and percentages. The test for the difference in continuous data was performed by using t-test or Mann-Whitney U test and Chi-square or Fischer-exact test for categorical data. The relative risk (RR) with 95% confidence interval (CI) and the number needed to harm (NNH) were calculated for determining the main factors associated with 30-day RH.

The study protocol was approved by MNRH Institutional Review Board in accordance with ethical standards on human experimentation and the Helsinki Declaration.

Results

There were 293 AIS patients (from 349 subjects) with IV-rtPA therapy who were discharged alive between study duration. After excluding patients who lost to follow up (55 patients), a total of 238 patients with 128 males (53.8%) were enrolled in this study. The mean age±standard deviation was 62.3±13.8 years. The common co-morbidities were hypertension (106 patients, 44.5%), diabetes (42 patients, 17.6%) and dyslipidemia (41 patients, 17.2%). The mean NIHSS, GCS and MRS at initial-admission were 13.3±5.2 points, 13.1±2.6 points and 3.8±1.3 points, respectively. The median (minimum-maximum, interquartile range) length of hospital stay of initial-admission was 6.0 (2-49, 6.0) days. In-hospital complications after received IV-rtPA occurred in 79 patients (33.2%). The most common complication was pneumonia (36 patients, 15.1%). Thirty patients (12.6%) had intra-cerebral hemorrhage, 27 patients (11.3%) had severe hypertension (need intravenous antihypertensive agent), and 33 patients (13.9%) needed ventilator support during initial-admission. Others baseline characters and in-hospital complications were shown in Tables 1 and 2.

The 30-day RH occurred in 24 patients (10.1%, 95%CI 6.3-13.9%) with median duration of 10.5 (2-29, 10) days after discharge. The common causes of 30-day RH were pneumonia which were found in 10 patients (41.6%), recurrent stroke (4 patients, 16.6%), CV event (4 patients, 16.6%) and others infection (4 patients, 16.6%), (Table 3). The me-

Table 1 Baseline characters of all patients and the comparison between those with and without 30-dayrehospitalized (n=238)

Baseline Characteristics	Total (n=238)		Rehospitalization				p-value	RR	95%CI
			No (n=214)		Yes (n=24)				
			Number	%	Number	%			
Male gender	128	53.8	112	87.5	16	12.5	0.19	1.72	0.76-3.86
Diabetes	42	17.6	39	92.9	3	7.1	0.49	0.67	0.21-2.13
Hypertension	106	44.5	96	90.6	10	9.4	0.77	0.89	0.41-1.92
Dyslipidemia	41	17.2	36	87.8	5	12.2	0.62	1.26	0.50-3.19
Previous stroke	53	22.3	46	86.8	7	13.2	0.39	1.44	0.63-3.28
Previous admission	26	10.9	23	88.5	3	11.5	0.79	1.16	0.37-3.64
Ischemic heart	11	4.6	10	90.9	1	9.1	0.91	0.90	0.13-6.05

Table 1 Baseline characters of all patients and the comparison between those with and without 30-day rehospitalized (n=238) (Cont.)

Baseline Characteristics	Total (n=238)		Rehospitalization				p-value	RR	95%CI
			No (n=214)		Yes (n=24)				
			Number	%	Number	%			
Stroke Type*									
Cardioembolic	96	40.3	85	88.5	11	11.5	0.26		
Large vessel	48	20.2	41	85.4	7	14.6			
Small vessel	94	39.5	88	93.6	6	6.4			
Discharged by refer	60	25.2	49	81.7	11	18.3	0.02	2.51	1.19-5.30
Mean age - year	62.3±13.8		61.9±13.6		66.4±14.1		0.13		
Mean NIHSS**	13.3±5.2		13.3±5.0		14.9±5.9		0.12		
Mean GCS**	13.1±2.6		13.2±2.6		12.3±2.5		0.12		
Mean MRS**	3.8±1.3		3.9±1.3		3.9±1.4		0.94		
Median Hospital stay-Day	6.0	6.0	5.0	3.0	6.0	6.0	0.10		

Remark: * classified as TOAST classification,

** evaluated at time of admission

- NIHSS = National Institute of Health stroke scale
- GCS = Glasgow coma score
- MRS = modified Rankin scale

Table 2 In-hospital complications of all patients and the comparison between those with and without 30-day rehospitalized (n=238)

Initial-Admission Complications	Total (n=238)		Rehospitalization				p-value	RR	95%CI
			No (n=214)		Yes (n=24)				
			Number	%	Number	%			
All complications	79	33.2	65	82.3	14	17.7	<0.01	2.82	1.31-6.06
Pneumonia	36	15.1	25	69.4	11	30.6	<0.01	4.75	2.31-9.76
ICH	30	12.6	22	73.3	8	26.7	<0.01	3.47	1.63-7.39
Severe hypertension*	27	11.3	26	96.3	1	3.7	0.28	0.34	0.05-2.42
Atrial fibrillation	72	30.3	64	88.9	8	11.1	0.35	1.15	0.52-2.57
Intubation	33	13.9	28	84.8	5	15.2	0.29	1.63	0.66-4.08

Remark: ICH = intracerebral hemorrhage

* need intravenous antihypertensive agent

Table 3 Cause of 30-dayrehospitalized and death rate in acute ischemic stroke patients with thrombolytic treatment (n=24)

Cause	Rehospitalization (n=24)		Death (n=9)	
	Number	%	Number	%
Pneumonia	10	41.6	4	44.4
Recurrent Stroke	4	16.6	1	11.1
Cardiovascular Event	4	16.6	2	22.2
Sepsis	2	8.3	1	11.1
Others Infection	2	8.3	0	0.0
Extracranial Bleeding	2	8.3	1	11.1

dian length of hospital stay for 30-day RH was 4.0 (1-17, 4) days, and 9 patients (37.5%) died during this admission. About 79.7% of RH (19 from 24 patients) occurred within 15 days after discharged. From those, pneumonia was an important cause for very early RH. Almost all patients with pneumonia (9 from 10 patients) were admitted between this duration.

Table 1 exhibited the analysis of baseline characters between patients with and without RH, there were no characters that related to 30-day RH, except discharged status. The patients who were discharged by refer had 30-day RH higher than those who were home discharged with RR= 2.51 (1.19-5.30) and NNH=9.1. The comparison of in-hospital complications during initial-admission between the subjects with and without RH was presented in Table 2. Pneumonia during initial-admission (RR=4.75 (2.31-15.81), NNH=4.15) and intra-cerebral hemorrhage after thrombolytic administrated (RR=3.47 (1.63-7.39), NNH= 13.9) were the significantly correlated factors for 30-day RH.

Discussion

RH among stroke survivors is common, resulting in high mortality, increased cost of healthcare, increased caregiver distress and worsening of patient status. Moreover, RH rate is used as an indicator for the quality and efficacy of in-hospital care in AIS. Therefore, understanding the reasons for RH after AIS can reduce the unnecessary RH event, economic impact, caregiver burden and patients mortality.

From the previous study, the significant proportion (20.0-40.0%) of the patients with stroke are rehospitalized within one years and those are highest in the first months (about 25.0%, or 5.0-10.0% of all RHs are within 1 month after initial event)[2,11]. The common reasons were pneumonia or respiratory illness (14.0-19.0%), recurrent stroke (13.0-16.0%), and CV event (6.0-17.0%)[2,12-15] which are similar to the findings of this study, in which pneumonia (44.1%), recurrent stroke and CV event were the three leading cause for RH. These results indicated that the common causes of RH in AIS patients were not different between those with and without thrombolytic therapy.

In this study, pneumonia and ICH during initial-admission were significantly associated with 30 day RH. This finding showed that in-hospital complications were the risk for RH[13,14,16]. This conclusion

was emphasized based on the finding from the analysis. The patients who were discharged by refer were more likely to be rehospitalized than those discharged to home, as a result of ineffective control of in-hospital complications. This finding supported that the management of in-hospital complication was very important issue for decreasing RH event even in the referred case.

From our study, the significant factors for RH were the potentially avoidable complications during initial-admission. Pneumonia, the leading cause of RH and death after stroke especially in acute setting, probably could be prevented through aspiration screening and feeding training, nasogastric tube insertion, and pneumococcal vaccine[17,18]. Additionally, careful adjustment of medications and well control CV risk factors before discharge may reduce the CV events and stroke recurrences.

The severity of stroke (according to NIHSS) and type of stroke (cardioembolic or large artery artherosclerotic subtype) were associated with 30-day RH in some previous studies.[12,16] However, these factors failed to present as a predictor for 30-day RH in this study. This argument occurred due to the inclusion criteria for thrombolytic treatment. Patients with large area of infarction were with high NIHSS and did not received thrombolytic agent, and thus were excluded from the study; whereas the others study included every patient with AIS.

There were some major limitations in this study. Firstly, the incidence of RH might be likely underestimated because some patients were lost to follow up (55 patients, 18.8%). These subjects might be admitted or died at local hospital, and were not included in the study. Secondly, we were unable to adjust other factors influencing RH such as home care, socioeconomic factors, medications after discharge (type and compliance), and rehabilitation. Finally, this study was performed in a tertiary care hospital. The results may not reflect the situation in all health facilities at all levels of health care system in Thailand. These limitations may be overcome in the future studies.

In conclusion, to reduce the number of unnecessary RH events among AIS patients (with or without thrombolytic therapy) especially those with post-stroke pneumonia or ICH, the prevention and management of of complications during initial-admission, aspirate precaution, postural drainage, well-trained rehabilitation and discharge planning should be introduced to reduce RH events.

Conclusions

The rate of 30-day RH in AIS patients with thrombolytic therapy in MNRH was 10.1% (95%CI 6.3-13.9%) and about 80.0% of these events occurred within first 15-days after discharged. Pneumonia (41.6%), recurrent stroke (16.6%) and CV event (16.6%) were the most common causes of RH. The significant associated factors for 30-day RH were the occurrence of pneumonia or ICH after thrombolytic treatment. General care and correction of complications during initial-admission were very important issues for reducing the RH rate among AIS patients.

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บทคัดย่อ: การเข้ารักษาในโรงพยาบาลซ้ำภายใน 30 วันในผู้ป่วยภาวะหลอดเลือดสมองตีบเฉียบพลันที่ได้รับการรักษาด้วยยาละลายลิ่มเลือด

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ภาวะหลอดเลือดสมองตีบเป็นโรคที่พบได้บ่อย นอกจากจะมีระยะเวลารักษาในโรงพยาบาลยาวนานแล้ว ยังพบปัญหาการกลับเข้ารักษาในโรงพยาบาลสูงโดยเฉพาะในช่วงเวลา 30 วันแรกหลังจากจำหน่าย การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาหาอัตราและปัจจัยที่เกี่ยวข้องกับการกลับเข้ารักษาในโรงพยาบาลภายใน 30 วัน ในผู้ป่วยภาวะหลอดเลือดสมองตีบที่ได้รับการรักษาด้วยยาละลายลิ่มเลือดในโรงพยาบาลมหาราชนครราชสีมา เป็นการศึกษาชนิด cohort แบบไปข้างหน้าในผู้ป่วยภาวะหลอดเลือดสมองตีบที่ได้รับการรักษาด้วยยาละลายลิ่มเลือดในโรงพยาบาลมหาราชนครราชสีมา โดยผู้ป่วยต้องเข้ารับการรักษาและจำหน่ายออกจากโรงพยาบาลในช่วงเวลาระหว่างเดือนมกราคม พ.ศ. 2554 ถึงธันวาคม 2557 เก็บข้อมูลของผู้ป่วยระหว่างเข้ารักษาในโรงพยาบาลครั้งแรก รวมถึงข้อมูลเกี่ยวกับการกลับเข้ารักษาซ้ำ และนำข้อมูลทั้งหมดมาวิเคราะห์ทางสถิติตามวัตถุประสงค์ของการศึกษา ผลการศึกษาพบว่ามีผู้ป่วยภาวะหลอดเลือดสมองตีบที่ได้รับการรักษาด้วยยาละลายลิ่มเลือดและจำหน่ายออกจากโรงพยาบาลในช่วงเวลาที่ทำการศึกษาทั้งสิ้นจำนวน 238 ราย เป็นเพศชายร้อยละ 53.8 เพศหญิงร้อยละ 46.2 ผู้ป่วยจำนวน 24 ราย (ร้อยละ10.1) กลับเข้าโรงพยาบาลซ้ำภายใน 30 วัน โดยร้อยละ 80.0 เกิดขึ้นภายใน 15 วันแรกหลังจากจำหน่าย สาเหตุที่พบบ่อยได้แก่ ภาวะปอดอักเสบ (ร้อยละ 41.6) การกลับเป็นซ้ำของโรคหลอดเลือดสมอง (ร้อยละ 16.6) และโรคหัวใจและหลอดเลือด (ร้อยละ 16.6) ผลจากการวิเคราะห์พบว่าผู้ป่วยที่เกิดภาวะปอดอักเสบหรือภาวะเลือดออกในสมองระหว่างการรักษาในโรงพยาบาลครั้งแรกมีความสัมพันธ์กับการกลับเข้าโรงพยาบาลซ้ำภายใน 30 วันอย่างมีนัยสำคัญทางสถิติที่ระดับนัยสำคัญ 0.05 โดยมีค่า relative risk เท่ากับ 4.75 (2.31-9.76) และ 3.47 (1.63-7.39) ตามลำดับ โดยสรุป การกลับเข้าโรงพยาบาลซ้ำภายใน 30 วันในผู้ป่วยภาวะหลอดเลือดสมองตีบที่ได้รับการรักษาด้วยยาละลายลิ่มเลือดในโรงพยาบาลมหาราชนครราชสีมา เท่ากับร้อยละ 10.1 โดยร้อยละ 80.0 กลับเข้าโรงพยาบาลภายใน 15 วันแรกหลังจากจำหน่ายสาเหตุที่พบบ่อยที่สุดคือ ภาวะปอดอักเสบ (ร้อยละ 41.6) โดยปัจจัยที่เกี่ยวข้องกับการกลับเข้าโรงพยาบาลซ้ำภายใน 30 วันคือ ผู้ป่วยเกิดภาวะปอดอักเสบหรือเลือดออกในสมองระหว่างการรักษาในโรงพยาบาลครั้งแรก

คำสำคัญ **การเข้ารักษาในโรงพยาบาลซ้ำ, ภาวะหลอดเลือดสมองตีบเฉียบพลัน, การรักษาด้วย ยาละลายลิ่มเลือด**