ORIGINAL ARTICLE

Clinical outcomes of acute stroke thrombolysis in neurologist and non-neurologist centres – A comparative study in Malaysia

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ABSTRACT

Background: Thrombolytic therapy with intravenous alteplase is a well-established treatment for acute ischaemic stroke (AIS). However, in Malaysia, treatment prescription is often limited by the availability of neurologists. The objective was to compare the outcomes of acute stroke thrombolysis therapy prescribed by neurologists in the Seberang Jaya Hospital (SJH) and non-neurologists in the Taiping Hospital (TH).

Methods: In this cross-sectional study, all AIS patients who received thrombolytic therapy in SJH and TH between January 2012 and September 2019 were included. Clinical data was extracted from admission records. The outcomes assessed were the percentage of patients who achieved excellent functional outcome at 3 months (modified Rankin scale of 0 to 1), rates of symptomatic intracranial haemorrhage (SICH), and mortality.

Results: A total of 63 AIS patients who received thrombolytic therapy were included, of which 37 patients (58.7%) were treated in SJH. The median NIHSS on admission was 12 in SJH and 11.5 in TH. In all 21.6% of patients from SJH and 30.7% of patients from TH achieved favourable functional outcome at 3 months (p=0.412). There were no significant differences between the two centres in terms of the rates of SICH (10.8% in SJH and 3.8% in TH, p=0.314) and 3-month mortality (24.3% versus 12.5%, p=0.203).

Conclusion: The 3-month functional outcomes and complication rates of stroke thrombolysis in hospitals with or without neurologists are not significantly different. Thus non-neurologist hospitals may be able to provide thrombolysis service to AIS patients safely and effectively.

KEYWORDS:
Acute ischaemic stroke, thrombolysis, functional outcome, non-neurologist

INTRODUCTION

Acute ischaemic stroke (AIS) is a devastating disease and one of the leading causes of disabilities worldwide. From 2010 to 2014, the incidence of stroke in Malaysia had increased from 65 to 187 per 100,000 population.[1] Thrombolytic therapy with intravenous recombinant tissue plasminogen activator (rtPA) within 4.5 hours of symptom onset has been shown to be an effective treatment for AIS. Patients who receive thrombolysis are 30 percent more likely to achieve excellent functional outcome (modified Rankin scale of 0 to 1) at 3 months compared to placebo.[2]

Unfortunately, the delivery of stroke thrombolysis service in Malaysia is often limited by the availability of neurologists. To date, the ratio of neurologists capable of performing thrombolysis serving in public hospitals to the Malaysian population is 1:1.4 million.[3] To counteract this disparity and to cope with the increasing stroke burden in Malaysia, there has been an advocacy for greater involvement of non-neurologists, i.e., general and emergency physicians in performing of stroke thrombolysis.[4] Emerging data based on short term outcomes appear to support this notion.

Based on a 2015 single center study on 49 AIS patients in Australia, A. Lee et al., reported that there was no significant difference in door to needle time, rates of symptomatic intracranial bleeding (SICH), and mortality between patients thrombolysed by neurologists versus stroke physicians.[5] In 2016, a larger multicentre study in Thailand reported that patients thrombolysed in hospitals without neurologists had lower National Institute of Health Stroke Scale (NIHSS) scores at discharge and lower inpatient mortality rate compared to patients treated in neurologist hospitals.[6] Based on these short term outcomes, both studies suggest that non-neurologists are able to thrombolyse AIS patients safely and effectively. Data comparing long term functional outcomes in thrombolysis prescribed by neurologists and non-neurologists are still very limited.

The primary objective of this study was to evaluate and compare the 3-month functional outcomes of thrombolytic therapy between hospitals with and without on-site neurologists. The secondary objective was to assess the door-to-needle time and complication rates of thrombolysis service in both hospitals.

METHODS

This study was conducted in Seberang Jaya Hospital (SJH) and Taiping Hospital (TH), two district hospitals in the

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northern region of peninsular Malaysia which are designated as Primary Stroke Centres (PSC). Both hospitals have similar bed capacity and numbers of medical staffs. They are equipped with emergency departments with streamline stroke activation protocols, 24/7 radiology services to provide rapid diagnostic imaging for stroke patients, intensive care support, and physicians trained in the administration of stroke thrombolysis.[7] In SJH, thrombolysis is prescribed by an in-house neurologist (referred herewith as the neurologist hospital) whilst in TH, as there is no on-site neurology support (referred as the non-neurologist hospital), stroke thrombolysis is led by a geriatrician. A comparison of both hospitals is shown in Table I.

In this cross-sectional study, we included all AIS patients who were admitted and given thrombolytic therapy in the SJH and the TH between 1st January 2012 and 1st September 2019. All AIS patients had urgent brain computed tomography (CT) scans on arrival and eligibility for thrombolysis and were assessed clinically. Patients who had onset of stroke within 4.5 hours with no exclusion criteria according to the protocol were given intravenous alteplase 0.9mg per kilogram. Patients with stroke of large vessel occlusion and received endovascular thrombectomy were specifically excluded from the study. All thrombolysed patients were transferred to the respective intensive care or acute stroke units for close monitoring. CT scans of the brain were repeated 24 hours post-thrombolysis and when required thereafter. All patients underwent in-patient rehabilitation during hospital stay and received antiplatelet (or anticoagulant if atrial fibrillation was detected) and statin therapy upon discharge. They were followed up later in clinics at three months.

The lists of AIS patients who received thrombolysis therapy were obtained from the National Stroke Registry of Malaysia. Relevant demographic and clinical data were extracted from admission records and patient charts. Stroke subtypes were classified according to clinical presentation using the Oxfordshire Community Stroke Project (OCSP) classification system, which had been shown to carry prognostic significance in stroke recovery.[8] The efficiency of thrombolysis service is determined by assessing the door to needle time.

The functional outcome measured was the modified Rankin scale (mRS) at three months. MRS was determined by trained personnel in the respective centers during clinic follow ups. For patients who were unable to return for clinic assessment, the mRS was ascertained by structured phone interviews using the validated revised version of simplified Modified Rankin Scale Questionnaire (smRSq).[9] Safety outcomes assessement included symptomatic intracranial haemorrhage (SICH), other major bleeding that required blood transfusion, minor bleeding, inpatient mortality and overall mortality at day 90. SICH followed the ECASS III definition of any extravascular blood in the brain within 36 hours that was associated with an increase of 4 points or more in NIHSS score or leading to death.[2]

The data were analysed using the SPSS version 22. When comparing between the two centers, independent student *t* test was used for analysis of continuous variables while Chi-square or Fisher's exact test (when appropriate) was used for categorical data. An alpha value of 0.05 was considered statistically significant. To ascertain the effect of treating centres on the key clinical outcomes, logistic regression was performed using variables which carry univariate significance of $p<0.10$.

Ethical approval for this study was obtained from the Malaysia Research Ethics Committee. (NMRR 08-16323189)

RESULTS

Of the 63 AIS patients given thrombolytic therapy 37 patients (58.7%) were treated in the SJH whilst 26 patients (41.2%) were treated in the TH. There was no significant difference between the two patient cohorts in terms of demographic and baseline characteristics (Table II). Most of the stroke patients were relatively young, with the mean age of 58.2 and 54.0 years in SJH and TH respectively and 54.1% and 61.5% were men. Hypertension and diabetes were the two commonest risk factors associated with stroke in the study population. In all 13.5% and 7.7% of patients were found to have atrial fibrillation at presentation.

The median NIHSS scores on admission were 12 (interquartile range, IQR 9 to 18) in SJH and 10.5 (IQR 9 to 14) in TH. More than half of the AIS patients fell within the moderately severe stroke category (NIHSS 9 to15). There were relatively more lacunar strokes and mild strokes (NIHSS of 1-8) in TH compared to SJH (p=0.640). No patient with posterior circulation infarct was thrombolysed in both the cohorts. Majority of the stroke patients (60.3%) received thrombolysis therapy after 180 minutes from the onset of stroke symptoms. The door to needle time in the neurologist hospital was shorter compared to the non-neurologist hospital (112 minutes versus 130.6 minutes), the difference however, was not statistically significant (p=0.538).

The median NIHSS scores on discharge were 10 (IQR 6-15) for SJH and 7.5 (3 -12) for TH, representing a mean reduction of NIHSS scores by 2 and 3 points respectively post thrombolysis. On average, the stroke patients in SJH spent 4 days in the hospital compared to 7 days for those in the TH. At 3 months follow up post thrombolysis, 21.6% of patients from SJH and 30.7% of patients from TH achieved excellent outcomes with mRS of 0 to 1. However, the difference was not statistically significant (p=0.412). The overall distribution of mRS scores is shown in Figure 1 and the comparison of clinical outcomes is shown in Table III.

In terms of safety outcomes, the rate of symptomatic intracranial bleeding within 36 hours of thrombolysis was 10.8% in SJH and 7.7% in TH (p=0.678). One patient from both the SJH and the TH required neurosurgical intervention for intracranial bleeding. There was no incidence of major extracranial bleeding in both the hospitals. Four patients from SJH suffered from minor bleeding complications, for instance cutaneous bruising that did not require blood transfusion. In all seven patients from the SJH and three patients from the TH passed away during index hospitalisation, mostly as a result of massive cerebral infarct and oedema. The overall mortality rate at three months was 24.3% in the SJH and 12.5% in the TH. Nonetheless, the difference was not statistically significant (p=0.546).

Table I: Comparison of hospital characteristics

Hospital characteristics	Seberang Jaya Hospital	Taiping Hospital
Hospital level	District with specialist	District with specialist
Bed size	312	608
Catchment areas	Seberang Jaya, Bukit Mertajam	Larut Matang, Kerian, Kuala Kangsar,Ulu Perak
Population	452,720	634,146
Presence of neurologist	Yes	No
Number of medical specialists	14	14
Number of emergency physicians	5	5
Number of CT scanner	1	1

Table II: Demographic and baseline characteristics of the patients

Baseline characteristics	Seberang Jaya Hospital (N=37)	Taiping Hospital (N=26)	p value[a]
Age, year (mean ± SD)	58.2 ±11.5	54.0 ±13.4	0.127[b]
Male sex, n (%)	20 (54.1)	16 (61.5)	0.552
Diabetes, n (%)	16 (43.2)	13 (50.0)	0.293
Hypertension, n (%)	26 (70.3)	19 (73.1)	0.808
Atrial fibrillation, n (%)	5 (13.5)	2 (7.7)	0.469
Smoker, n (%)	11 (29.7)	9 (34.6)	0.682
Recurrent stroke, n (%)	5 (13.5)	4 (15.4)	0.834
Prior use of antiplatelet, n (%)	8 (21.6)	10 (38.5)	0.145
NIHSS			
Median (IQR)	12 (9 -18)	10.5 (9 -14)	0.262[b]
Minimum	7	6	
Maximum	25	22	
stroke subtype, n (%)			0.581
TACI	8 (21.6)	3 (11.5)	
PACI	18 (48.6)	14 (53.8)	
LACI	11 (29.7)	9 (34.6)	
stroke severity, n (%)			
mild (NIHSS 1-8)	6 (16.2)	5 (19.2)	0.640
moderate (NIHSS 9-15)	20 (54.1)	16 (61.5)	
severe (NIHSS 16-42)	11(29.7)	5 (19.2)	
onset to treatment time (in minute)			
mean, SD	203.1 ± 53.9	201.2 ± 59.5	0.645[b]
<180 min, n (%)	15 (40.5)	10 (38.5)	0.868
≥180 min, n (%)	22 (59.5)	16 (61.5)	
Door to needle time (in minute)			
Mean, SD	112.1 ± 45.4	130.6 ± 52.6	0.538[b]

[a]unless stated otherwise, p values were derived from Chi Square test for independence
[b]Independent samples t test
TACI, total anterior circulation infarct. PACI, partial anterior circulation infarct. LACI, lacunar infarct.

Table III: Clinical outcomes of stroke thrombolysis

Outcome measurements	SJH (N=37)	TH (N=26)	p value
NIHSS on discharge, median (IQR)	10 (6-15)	7.5 (3 -12)	0.132
Length of stay, mean ± SD	6.86 ± 9.67	9.15 ± 9.82	0.362
Patients with excellent recovery, mRS 0-1 at 3 months, n (%)	8 (21.6)	8 (30.7)	0.412
Patients with independent recovery, mRS of 0-2 at 3 months, n (%)	13 (35.1)	13 (53.3)	0.141
Symptomatic Intracranial haemorrhage, n (%)	4 (10.8)	2 (7.7)	0.678
Minor bleeding complications, n (%)	4 (10.8)	0 (0)	0.245
Inpatient mortality, n (%)	7 (18.9)	3 (11.5)	0.430
Mortality at 3 months, n (%)	9 (24.3)	3 (11.5)	0.203

[a]unless stated otherwise, p values were derived from Chi Square test
MRS modified Rankin scale

Table IV: Logistic regression analysis on factors associated with poor clinical outcomes and symptomatic intracranial haemorrahge

Clinical outcomes	Adjusted odds ratios for Non-neurologist centre (95% CI)	P value
Poor recovery, mRS 4-6	0.62 (0.21, 1.80)	0.375
Symptomatic Intracranial haemorrhage	0.72 (0.12, 4.30)	0.717

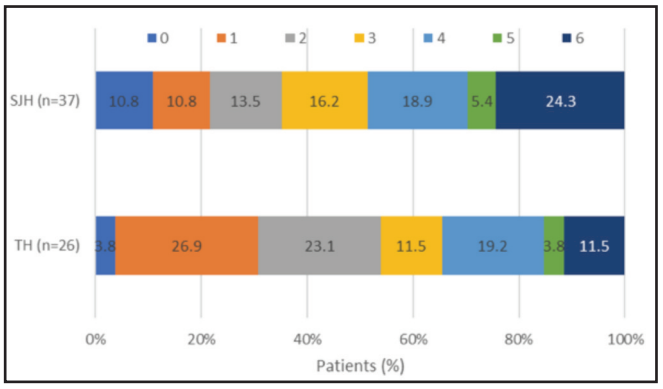

Fig. 1: Distribution of Scores on the Modified Rankin Scale.

In the univariate logistic regression analysis, NIHSS score on admission was the only independent predictors of poor functional outcome, defined as mRS 4 to 6. (p=0.095). After adjusting for this, we demonstrated that thrombolysis treatment in non-neurologist centre is not a predictor of poor functional recovery (odds ratios [OR] 0.62, 95% confidence interval [95%CI] 0.21, 1.80), and also SICH (OR 0.72, 95% CI 0.12, 4.30). (Table IV)

DISCUSSION

In the advent of endovascular thrombectomy treatment, with all its positive acclaim in treatment of acute stroke, intravenous thrombolysis with alteplase remains the mainstay of treatment, especially in developing countries like Malaysia. The existence of a clear selection protocol, in addition to the relative ease of administration without the need of highly skilled personnel or equipment, have led to a gradual uptake of thrombolysis service in more hospitals in Malaysia, including district hospitals without neurologists. Nonetheless, there is no data from Malaysia thus far to examine the safety and efficacy of thrombolysis service provided in non-neurologist centres.

To our knowledge this is the first study in Malaysia that directly compares the clinical outcomes of stroke thrombolysis between hospitals with and without neurologists. It is an important study as all thrombolysed patients were followed up for functional outcomes at three months post stroke. In this study, there were no significant differences in terms of door to needle time, NIHSS on discharge and the proportion of patients achieving favourable recovery between centres with neurologist and without. Most importantly, there were no excess in rates of SICH and inpatient mortality in the non-neurologist centre. These findings are consistent with previous studies comparing stroke outcomes post thrombolysis lead by neurologist versus non-neurologist.[5]

In order to explain these findings, we postulated that the overall system of thrombolysis service and post-thrombolysis care are more important factors than the specialties of the prescribers. In the past, AIS patients may be best managed by neurologists to ensure that an accurate diagnosis can be established. With increasing accessibility to comprehensive training in stroke assessment and thrombolysis via the Angel's initiative, non-neurologists nowadays are better equipped to initiate the needed urgent intervention for stroke.[10] Admittedly, the confidence and duration of training of the treating physicians such as the number of stroke cases seen in a year and the overall experience in caring for stroke patients were not measured in this study. Equally important are the aspects of post-acute care in stroke units and quality of rehabilitation, which have been shown unequivocally important to reduce stroke morbidity and improve functional outcomes in stroke patients.[11] All these are pertinent confounders in determining the long-term functional outcomes of stroke patients. However, it was beyond the scope of this study to examine and compare all aspects of peri-thrombolysis care in both the hospitals.

The findings of the present study should be interpreted with caution due to some inherent limitations. Firstly, this was a retrospective, observational study. Randomisation was not possible as patients will always seek medical attention at the nearest stroke centre. However, the two district hospitals were comparable in terms of manpower and ancillary services available. The demographics of our patients and stroke severity in both centres were also not significantly different. Secondly, the sample size of 63 was small and may be underpowered to detect any significant differences in terms of functional outcomes and complication rates. Nonetheless, it did shed light on the trend of outcomes. With no signal of safety concern, the thrombolysis service will continue and more data will be prospectively collected to paint a clearer picture.

CONCLUSION

Hospitals without in-house neurologists may be able to provide thrombolysis service to AIS patients safely and effectively. In this context, the absence of an on-site neurologist should not be a barrier to setting up thrombolysis service in district hospitals. In fact, the key to successful delivery of thrombolysis service lies with active participation of all parties including emergency physicians, general physicians and radiologists. A streamlined stroke activation pathway needs to be established, from pre-notification to ambulance transportation, rapid stroke assessment and priority imaging until the administration of thrombolysis. In addition, there should be proper post-acute care facilities to monitor patients post thrombolysis, together with a multidisciplinary team for stroke rehabilitation. Finally, as this study was essentially a single centre experience, more large-scale studies involving multiple centres are needed in order to verify this finding.

DISCLOSURE

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Conflict of Interest: None

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