ORIGINAL ARTICLE

Outcome of acute ischaemic stroke patients after intravenous alteplase in Hospital Universiti Sains Malaysia

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ABSTRACT

Introduction: Intravenous (IV) thrombolysis with recombinant tissue plasminogen activator (rt-PA) is effective in treating acute ischaemic stroke. Our primary objective is to assess the outcome of these acute ischaemic stroke (AIS) patients after IV alteplase with the modified Rankin scale (mRS).

Methods: This is a cross-sectional study in which patients receiving IV alteplase in Hospital Universiti Sains Malaysia, from January 2017 to April 2020 were recruited. Demographical data, National Institutes of Health Stroke Scale (NIHSS) scores, door-to-needle time were recorded. Modified Rankin scale (mRS) scores were evaluated at 90 days after initial therapy. Good and poor functional outcomes were defined as 0-2 and 3-6, respectively.

Results: A total of 30 patients were included in the study with a mean age of 59±11.47 years old. 76.7% of them were male and the rest were female. From the study, onset-to-needle time was 197.47±51.74 minutes, whereas door-to-needle time was 120.93±53.63 minutes. Seventeen (56.3%) patients achieved a favourable score of 0-2 on the mRS at 90 days after treatment. Haemorrhagic transformation occurred in eight (26.7%) of the patients with a mortality rate of 13.3%.

Conclusion: 56.7% of our patients showed improvement in the mRS at 90 days post thrombolysis for AIS. Higher baseline NIHSS scores and diabetes mellitus were associated with poorer functional outcomes after thrombolysis.

KEYWORDS:
Acute ischaemic stroke, rt-PA, door-to-needle time, functional outcomes, thrombolysis

INTRODUCTION

Stroke is one of the leading non-communicable diseases that carry a heavy social and economic impact on individuals and their immediate families.[1] Thus, it has the most significant burden of disease, based on the disability-adjusted life years.[2] It is estimated that 14 million people worldwide will suffer their first stroke and 80 million live with the burden of stroke. Stroke also accounts for 116 million years of healthy life lost to the disease.[1] This equates to roughly 14.7 million disability-adjusted life years affecting patients aged 20 to 64 years old, with the majority occurring in the developing countries.[3]

In Malaysia, stroke is one of the top ten causes for hospitalisation,[2] and the mean age of stroke patients in Malaysia is 62.5 years.[4] With a population of approximately 32.5 million in 2019, a majority (69.8%) of them fall into the 15 to 64 years old age group.[5] This increased ageing of the population indirectly leads to a higher number of stroke cases and an associated increase in the healthcare expenditure.

Management of acute ischaemic stroke (AIS) had undergone three stages of evolution, including the introduction of intravenous (IV) thrombolysis. Recombinant tissue plasminogen activator (rt-PA) is an IV thrombolysis for AIS, was licensed to be used since 1996 following the results from the National Institute of Neurological Disorders and Stroke trials.[6] The efficacy of the rt-PA treatment has been shown to improve functional outcomes of patients receiving the therapy within three hours of the onset of the symptoms. Functional outcomes of stroke patients are measured with the modified Rankin scale (mRS) and a score of 0 to 1 is considered as a favourable outcome, whereas a score of 0 to 2 means that the patient is alive and independent.[7,8] International guidelines unanimously agreed upon the safe and effective therapeutic window for treating AIS patients within 4.5 hours from onset of symptoms.[9,10] This study aims to evaluate the outcomes of AIS patients from January 2017 to April 2020. The onset-to-needle and door-to-needle time were also analysed.

METHODS

This cross-sectional study was approved by the Human Research Ethics Committee of Universiti Sains Malaysia (JEPeM), Kubang Kerian. Data from medical records were collected from January 2017 to April 2020.

This article was accepted: 31 September 2021
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The inclusion criteria were all AIS patients who presented through the Emergency Department (ED) and received IV alteplase therapy within 4.5 hours of symptoms onset. The demographic data included the age, gender, ethnicity and underlying medical comorbidities of patients. The timing of the onset of symptoms to the administration of IV alteplase (incident-to-needle time) and the registration time at the ED to the treatment time (door-to-needle) were also collected. The door-to-needle time is inclusive of assessment, stabilising and ordering CT scan for the patient from ED, reviewing the CT scan by the radiologist and neurologist before the administration of the treatment. Comorbidities like diabetes mellitus, hypertension, atrial fibrillation and underlying ischaemic heart disease were also included.

Patients received the standard dose of 0.9mg/kg IV alteplase (maximum of 90mg). The initial dose of 10% was administered as a bolus dose and the remaining 90% was a continuous infusion over one hour. Patients' mRS at the point of treatment were also assessed and compared against their respective mRS at 90 days post-therapy during follow-up at the Neurology Clinic or telephone interview with the patient or caregiver. A mRS of 0-2 was considered as a good clinical outcome, whereas a score of 3-6 was considered as a poor outcome.

Patients who developed haemorrhagic transformation post-therapy were managed accordingly and classified as a complication of the IV alteplase therapy. Symptomatic or fatal haemorrhagic transformation is also known as symptomatic intracerebral haemorrhage (SICH). SICH was defined as local or remote parenchymal haemorrhage within 36 hours posttreatment associated with deterioration of four points or more based on the National Institutes of Health Stroke Scale (NIHSS) or from the lowest NIHSS value between baseline and 24 hours or leading to death.[11] Mortality due to other causes was also recorded.

Data of the study was analysed using the IBM SPSS Statistics version 24. The numerical values seen in the tables are expressed as mean (standard deviation, SD) and percentages. Association between the variables and functional outcomes were analysed using the independent Student's t-test, Chi-square or Fisher's exact test. A p-value of <0.05 was considered as statistically significant. To determine the predictors of functional outcome, multiple logistic regression analysis was performed.

RESULTS

The demographic data of the patients recruited during the study period is shown in Table I. A total of 30 patients received IV alteplase. The duration of the study was approximately 40 months; hence, the treatment frequency is less than 1 case per month. Hospital USM (USM) is one of two centres in the state of Kelantan, Malaysia that offers IV alteplase therapy.

Based on Table I, out of the 30 patients enrolled, 23 were males and seven were females. The mean age of the patients was 59 years old (SD±11.47), with the youngest patient at 36 years of age, whereas the oldest patient was 79 years of age. All the patients were Malays. Hypertension (56.6%) and diabetes mellitus (33.3%) form the major comorbid suffered by these patients. The mean onset time to treatment (incident-to-needle) was 197.47 minutes (SD±51.74), whilst the door-to-needle time was 120.93 minutes (SD±53.63). All but one of the patients suffering from a stroke in the territories supplied by the middle cerebral artery, with the odd one out suffering from a posterior circulation stroke. A mean NIHSS score prior to IV alteplase was 10.60 (SD±4.61)

The mean mRS during admission was 3.43 (SD±1.331) and there was no significant difference with the mRS of 2.93 (SD±1.929) at 90 days after the therapy. Figure 1 shows the percentages of the patients based on their pre-treatment and post-treatment of mRS scores.

Table II shows a breakdown of all the variables assigned to two different outcomes, one being those with a good outcome (mRS 0-2)[10] and the other being a poor outcome (mRS 3-6). A total of 17 patients (56.7%) had a good outcome (mRS 0-2) at 90 days after the IV alteplase therapy in which 7 (23.3%) of them were able to return to pre-stroke functional activities. Patients with good outcomes have a pre-treatment NIHSS score of 9.53 (SD=4.78) compared to 11.89 (SD=4.05) in those who had a poor outcome.

A total of eight patients (26.7%) developed haemorrhagic transformation after the IV alteplase of which four (13.3%) passed away following the insult and four patients recovered with some functional outcome. Two patients suffered haemorrhagic transformation during the treatment but after 90 days, they were able to achieve good outcomes (p=0.049). The other four patients (13.3%) who had passed away were due to hospital-acquired pneumonia, acute coronary event, sepsis and the last patient passed away at home due to unknown causes, respectively. Table IV shows the breakdown of patients with haemorrhagic transformation according to year, with zero cases in 2020.

However, there were no statistically significant outcomes between the ages, gender, hypertension, area of infarct, incident-to-needle, door-to-needle before IV alteplase and the functional outcomes after 90 days of patients. Table III shows that for each increment in the pre-treatment NIHSS score, patients had 20% lower odds of achieving a good outcome (OR=0.80, 95%CI: 0.640, 0.995). Diabetes mellitus (p=0.034) and NIHSS scores (p=0.045) have a statistically significant association with the functional outcomes.

DISCUSSION

Thrombolysis in AIS is a relatively new service with limited experience among physicians in Malaysia, particularly in Hospital USM. Hospital USM had the stroke thrombolysis protocol since 2012 but very few patients had been thrombolysed. With the initiative of the acute stroke team in Hospital USM, the number of AIS patients being thrombolysed has increased slowly. Only 23.3% of our patients achieved a mRS of 0-1 (excellent outcome)[7] at 90 days post treatment from our study. This is comparatively lower than other published data in the Southeast Asia region, where the improvement ranges were from 26.1% to 59%.[12-15] European studies had achieved excellent outcomes ranging from 31% to 53%[16,17] whereas one study in the United States

Table I: Baseline characteristics of patients treated with IV rt-PA (n=30)

Characteristics	n (%) / mean (SD)
Age (years)	59.0 (11.47)
Gender	
Male	23 (76.7)
Female	7 (23.3)
Ethnicity	
Malay	30 (100.0)
Mode of transport to ED	
By Self	28 (93.3)
By Ambulance	2 (6.7)
Hypertension	17 (56.6)
Diabetes Mellitus	10 (33.3)
Ischaemic Heart Disease	2 (6.7)
NIHSS score pre rt-PA	10.60 (4.61)
Onset-to-treatment time	197.47 (51.74)
Door-to-needle time	120.93 (53.63)
Modified Rankin Scale (Admission)	
0-1	
0-2	7 (23.3)
3-6	23 (76.7)
Modified Rankin Scale (90 Days)	
0-1	7 (23.3)
0-2	17 (56.7)
3-6	13 (43.3)
Modified Rankin Scale at Admission	3.43 (1.331)
Modified Rankin Scale at 90 Days	2.93 (1.929)
Haemorrhagic Transformation	4 (13.3)
Minor haemorrhagic complications	4 (13.3)
Mortality	
Due to haemorrhage	4 (13.3)
Other causes	3 (10.0)
Area of Infarct	
Left Middle Cerebral Artery	18 (60.0)
Right Middle Cerebral Artery	11 (26.7)
Posterior Circulation	1 (3.3)

Table II: Analysis of factors determining functional outcome

Parameters	n (%) / mean (SD)		p-value
	Good Outcome (n=17)	Poor Outcome (n=13)	
Age (years)	57.18 (12.98)	61.38 (9.06)	0.328[a]
Gender			0.666[b]
Male	14 (46.7)	9 (30.0)	
Female	3 (10.0)	4 (13.3)	
NIHSS score pre rt-PA	9.35 (4.72)	12.23 (4.09)	0.091[a]
Onset to Needle (minutes)	190.94 (51.96)	206.00 (52.25)	0.439[a]
Door to Needle (minutes)	123.41 (64.17)	117.69 (37.95)	0.763[a]
Haemorrhagic Transformation			0.049[c]
Yes	2 (6.7)	6 (20.0)	
No	15 (50.0)	7 (23.3)	
Mortality			0.001[c]
Death due to SICH	0 (0.0)	4 (13.3)	
Death due to other causes	0 (0.0)	3 (10.0)	
No	17 (56.7)	6 (20.0)	
Hypertension			0.785[b]
Yes	10 (33.3)	7 (23.3)	
No	7 (23.3)	6 (20.0)	
Diabetes Mellitus			0.255[c]
Yes	4 (13.3)	6 (20.0)	
No	13 (43.3)	7 (23.3)	
Ischaemic Heart Disease			0.492[c]
Yes	2 (6.7)	0 (0.0)	
No	15 (50.0)	13 (43.3)	
Ischaemic Area			0.452[c]
Left MCA	10 (33.3)	8 (26.7)	
Right MCA	7 (23.3)	4 (13.3)	
Posterior Circulation	0 (0.0)	1 (3.3)	

[a]independent t-test, [b]Pearson chi-square, [c]Fisher Exact test

Table III: Multiple logistic regression of factors determining functional outcome

Parameter	β	p-value	OR	95% CI
Age	-0.04	0.360	0.96	0.88-1.05
NIHSS pre rt-PA	-0.23	0.045	0.80	0.64-0.99
DM	-2.60	0.034	0.08	0.01-0.82
HPT	1.35	0.214	3.85	0.29-32.36

Table IV: Breakdown of haemorrhagic transformation according to year

Year	Haemorrhagic Transformation	Total Number of Patients Receiving IV Alteplase
2017	2	6
2018	2	10
2019	4	10
2020	0	4

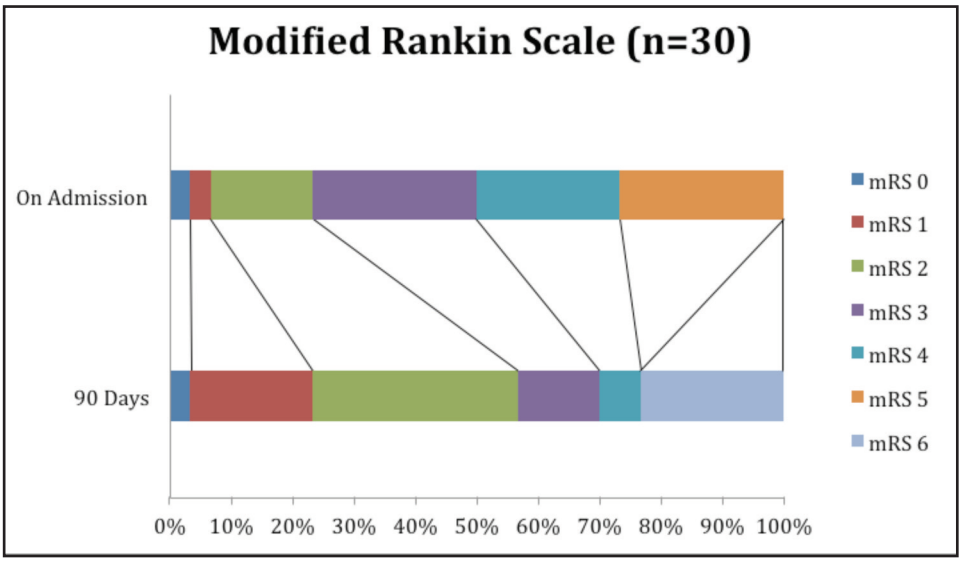

Fig. 1: Modified Rankin Scale on Admission and at 90 Days post IV rt-PA.

of America had achieved 78.2% of excellent outcome.[18] However, 56.7% of our patients had a good outcome with functional independence (mRS of 0-2). This is comparable with another local study at the University of Malaya Medical Centre where 55.6% of their patients had achieved a similar outcome.[13]

Many studies trying to predict the functional outcome of AIS patients.[19-21] For example, one local study found poor functional outcome was associated with higher baseline NIHSS scores and the presence of DM.[13] On the other hand, one Australian study found that age is a significant predictor of good functional outcomes independent of stroke severity.[22]

Symptomatic intracranial haemorrhage (SICH) is a major complication following thrombolysis.[23] In our study, 13.3% of our patients had SICH and this incidence was higher than the findings of a local study.[12,24] A study in Hong Kong had a much lower SICH rate of 4%.[25] Clinical trials such as NINDS and ECASS II had 6.4% and 8.8% incidence of SICH.[23] Published reports have identified a few risk factors for SICH, such as age more than 70 years old,[26] National Institute of Health Stroke Scale (NIHSS) more than 20,[27] diabetic patients with high serum glucose levels,[28] international normalized ratio (INR) ≥1.028 and history of coronary artery disease or atrial fibrillation.[29] Many risk factors and predictions have been proposed for the risk of SICH, including computerised tomography (CT) based scale, MRI-based technique and plasma biomarkers.[22]

In our study, the overall mortality rate at three-month was 23.3%, which is higher than regional studies that range from 3.2% to 15.0%.[12-15,25] However, SICH as the main cause of death (13.3%) is comparable to another study.[30] Our study also did not explore the risk factors associated with haemorrhage, which could be related to various factors such as the size of cerebral infarct, the ASPECT score at presentation, late-timing of alteplase infusion or other relative contraindications. The pathogenesis of intracerebral haemorrhage after thrombolysis are probably due to pre-existing microbleeds and leukoaraiosis, as the majority of patients had either diabetes or hypertension.[23]

The concept of "time is brain"31 has become more significant as shorter onset-to-needle time is associated with better functional outcomes.[32,33] Our onset-to-needle time was

197.47±51.74 minutes, which is longer than the guideline.[34] However, this result is comparable with a Malaysian study where the mean onset-to-needle time was 211 minutes.[13] Studies from Hong Kong and Vietnam had a shorter mean onset-to-needle time of 143 minutes,[15,25] whereas another study from Singapore had a median onset-to-needle time of 165 minutes.[12] Our door-to-needle time is at 120.93±53.63 minutes which is comparable to the Malaysian Stroke Registry's time of 132 minutes.[4]

Nevertheless, the time is still beyond the target in the guideline.[34] One of the major proponents for reduced mortality and improved outcomes is the door-to-needle time. Patients receiving IV alteplase within 45 minutes have a lower mortality rate. Conversely. every increment of 15 minutes up to 90 minutes of door-to-needle time is significantly associated with worse outcomes.[32]

In order to improve the time to thrombolysis, proven strategies have been identified[35] and separated into three distinct categories: pre-hospital, in-hospital and post-treatment decision strategies. The pre-hospital component is mainly directed at public education, stroke awareness and early arrival to the hospital. In Malaysia, stroke awareness is segregated into urban and rural areas, whilst the city dwellers are competent in their knowledge[36] and the opposite is for those coming from the rural areas.[37] Recognition of stroke symptoms is one of the crucial keys to early access to medical therapy.[38] This is followed by in-hospital strategies inclusive of a fast-track system for thrombolysis.[12,39] Easy availability of IV alteplase and simplification of informed consent prior to treatment at the ED must also be streamlined.[35]

There are several limitations to our study. Firstly, it is a cross-sectional study and information was taken from medical records and follow-up notes. Thus, interobserver variability of the mRS score would remain a substantial bias.[40] Secondly, the small sample size (n=30) from a single-center does not show the complete picture of the disease. Finally, the racial composition of the patients was 100% from the Malay ethnic group, which does not reflect the national population.

CONCLUSION

Our study has shown that 56.7% of our patients showed improvement in the mRS at 90 days post IV alteplase for AIS patients in Hospital USM, which is on par with Malaysian reports. However, as a newly established service, we had a SICH complication rate of 13.3%. In addition, higher baseline NIHSS scores at presentation and the presence of diabetes mellitus were associated with poorer functional outcomes.

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