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Stroke thrombolysis in the Philippines

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Abstract

Background & Objective: Currentlythere is limitedintervention for acute ischemic stroke. Recombinant tissue plasminogen activator (rTPA) has been approved for immediate recanalization after a steno-occlusive lesion of cerebral vessels. rTPA has shown its efficacy and safety from several clinical trials. The present study reports our experience with intravenous rTPA from several centers in the Philippines.*Method:*This is a retrospective cohort study consisting of 157 patients who qualified to receive rTPA following the NINDS trial inclusion and exclusion criteria. The primary outcome is in-hospital and 3-months mortality. Other outcome measures were determined: intracranial hemorrhage secondary to hemorrhagic conversion and functional outcome as measured by modified Rankin Scale. Additionally, standard dose (0.9mg/kg) was compared to low dose (0.6mg/kg) of rTPA in terms of mortality, intracranial bleeding and functional outcome.*Results:*The in-hospital mortality was seen in 23 (14.6%) and total death within 3 months was 18.3%. Independent patient (mRS 0-2) was seen in 69 (51.1%) at discharge and 95 (73.1%) at 3 months. Intracranial bleeding due to asymptomatic hemorrhagic transformation occurred in 39 (24.8%) and symptomatic hemorrhagic transformation was seen in 19 (12.1%).
Conclusion: Comparing our results with SITS-MOST and Cochrane collaborations, our data showed that we have more independent patients however death and intracranial bleeding was noted to be high in our cohort of patients. Additionally, the study showed more independent patients in the low dose group.

Keywords: thrombolysis, outcome, Asia, Philippines

INTRODUCTION

Stroke affects approximately 15 million people worldwide every year; around 9 million are Asians.[1] In the Philippines, the estimated prevalence of stroke is 9.0[21]/1,000[2], where 70% comprises of ischemic stroke while 30% of which are hemorrhagic stroke.[3] It is also one of the most common causes of disability worldwide.[4] Intravenous recombinant tissue plasminogen activator (IV rtPA) has been utilized since 1996 following the NINDS trial as the primary agent capable of reversing or reducing the extent of neurologic injury if given within 3 hours of onset of acute ischaemic stroke[5]; subsequent clinical trials have shown the benefit of rTPA administration up to 4½ hours after stroke onset.[6] Presently, it is the only approved agent for intravenous thrombolysis in most parts of the world.[7]

The rate of IV rtPA use for stroke varies from 1.3-9% among Asian countries.[8] Currently, more than 12000 stroke patients are estimated to receive this therapy each year, corresponding to 5% to 6% of patients with ischemic stroke, where dose ranges from 0.6 to 0.9mg/kg.[9-10] Several hospitals in East Asia and Southeast Asia have adopted the lower dosage and this makes comparison of outcomes quite challenging.[8]

In the Philippines, the use of IV rtPA was approved in 1999. However due to its prohibitive cost, the utilization has been significantly limited. Through a program provided by the Department of Health of the Philippine government, its availability can now be accessed for free since 2015.[11]This paper aims to describe the demographic features and clinical outcomes of stroke patients who received IV rTPA from 2014 to 2016. Additionally, the factors associated with

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bleeding, mortality and functional outcome at three months were likewise determined. The availability of these data for physicians who wish to use IV rTPA may alleviate their apprehension regarding adverse reactions and further help in the decision-making in carrying out IV thrombolysis for Filipino patients.

METHODS

This is a retrospective cohort study of patients who underwent intravenous thrombolysis with rTPA from 10 participating institutions from 2014 to 2016. The indications and contraindications were observed following the NINDS trial in the administration of IV rTPA.[5]The decision on the dose of rTPA, ranging from 0.6mg to 0.9 mg/kg body weight was left to the discretion of the attending physician. For standard dose of 0.9mg/kg, a 10% bolus was given for 1 minute and the remaining is given over 60 minutes. In some institutions 0.6mg/kg dose was utilized, 15% IV bolus is given within 1 minute and the remaining was infused over 60 minutes. Sonothrombolysis (rTPA + transcranial Doppler ultrasound continuous insonation) was likewise carried out in one institution.

The demographic features were gathered such as age, sex and vascular risk factors. The different vascular risk factors were defined as follows: arterial hypertension (BP >160/90 mmHg or on antihypertensive medications), diabetes mellitus (elevated fasting blood glucose or HbA1c 7.5% and above or on hypoglycemic medications), hypercholesterolemia (blood cholesterol >220mg% or on lipid lowering medications, elevated triglyceride levels and low density lipoprotein levels), presence of atrial fibrillation (demonstrated by EKG and 24-holter monitoring) coronary artery disease (abnormal EKG findings and/or elevated troponin-I), current and previous smokers (patients who smoke more than 10 sticks per day for more than a year) and significant alcohol intake (>30 grams of ethanol per day). The weight of the patients was only estimated because portable weighing scale is not readily available in most centers.

The primary outcome determined were in-hospital and 3 months mortality. Functional outcome was assessed with modified Rankin scale (mRS)[12,13]at three months either by patient evaluation in the clinic or by telephone interview. The mRS was dichotomized as follows: 0-2 independent, 3-5 dependent. Additional outcome measures were asymptomatic bleeding seen on CT scan done 24 hours after thrombolysis, and symptomatic intracranial bleeding associated with increased in NIHSS by four points at any time after thrombolysis and confirmed by non-contrast CT scan (NCCT). Bleeding from other parts of the body were also determined. Following the standards set by the American Heart Association, the timelines as the onset of stroke to door time, door to stroke team, door to CT scan and door to drug administration were compared.[14] The National Institute of Health Stroke Score (NIHSS)[15] on admission and 24 hours post thrombolysis was compared. Mortality rate, bleeding episodes and mRS of patients who received standard dose of rTPA (0.9mg/kg) were compared with the low dose (0.6mg/kg). The thrombolysis rate for the 3-year period was likewise calculated. Finally, in-hospital and 3 months mortality, mRS at 3 months, asymptomatic intracranial bleeding following CT scan 24 hours after thrombolysis, and symptomatic intracranial bleeding due to hemorrhagic conversion were compared with the Cochrane Collaboration[16] and the SITS-MOST project.[17]

Determination of factors associated with the outcomes of interest was analyzed using univariate and multivariate statistics. In the multivariate analysis, multiple logistic regression was utilized. Backward LR elimination was done to determine factors that were significantly associated with the outcome. Level of significance was set at alpha=0.05.

RESULTS

A total 157 patients out of 11,874 stroke patients qualified to receive intravenous thrombolysis were included in the study. There were more males than females, and about one third were smokers, and/or alcoholic drinkers. Mean age was 60 years old (SD±13). The majority of patients were hypertensive, comprising more than four-fifths of the total population; dyslipidemia was infrequent (Table1).

Mean duration from onset of presenting symptom to door was 94 (SD±65) minutes and from door to administration of thrombolysis was 97(SD±51) minutes.

Pre-thrombolysis treatment NIHSS was a mean of 12.7 and post-thrombolysis treatment NIHSS 9.9. The difference was statistically significant. In-hospital mortality rate post-thrombolysis treatment was 14.6% and within three months total mortality rate was 18.3% after discharge. Those alive, mRS showed that slightly more than

Table 1: Profiles of stroke patients (n=157)

Characteristic	n (%)
Sex, Male	97 (61.8)
Civil status	
Single	19 (12.1)
Married	116 (73.9)
Widowed	22 (14.0)
Risk Factors	
Hypertension	131 (83.4)
Alcohol drinker	53 (33.8)
Smoker	50 (31.8)
Diabetes mellitus	45 (28.7)
Atrial fibrillation	31 (19.7)
Previous stroke	22 (14.0)
CAD	15 (9.6)
Dyslipidemia	13 (8.3)

half were classified as independent on discharge, and the number increased to about three-fourths by three months.

A little less than one-fourth developed asymptomatic intracranial hemorrhage (and more than one-tenth had symptomatic intracranial hemorrhage (Table 2).

Factors associated with in-hospital mortality and within 3 months post-discharge were analyzed. Univariate analysis showed that only intracranial hemorrhagic transformation, symptomatic and asymptomatic were significantly associated with in-hospital mortality.

Finally we looked into factors affecting mortality within 3 months after hospital discharge. Multivariate analysis showed that diabetes mellitus (DM), symptomatic hemorrhagic transformation and initial NIHSS during admission were significantly associated with mortality anytime within three months. Controlling for each of the variables related with mortality, those with DM had more than 3 times the odds of dying compared to those without DM; those who presented with symptomatic hemorrhagic transformation had more than 20 times the odds of dying compared to those who did not; and lastly, for every one unit increase in the NHISS on admission, the odds of dying increased by 16%, (Table 3). A comparison between the standard dose (0.9mg/kg) and the low dose (0.6mg/kg) was carried out. (Table 4) There was no significant difference between these dosages as to mortality, intracranial bleeding. However, more independent patients were seen in the low dose group.

Table 5 shows the comparative data with Cochrane collaboration and SITS-MOST experience. The Philippine cohort showed a higher proportion with mRS 0-2; mortality and symptomatic hemorrhage were also found to be increased.

From a total of 11,874 acute ischemic stroke from 10 institutions 157 patients received rTPA from 2014-2016 with thrombolytic rate of 1.4%.

DISCUSSION

Our study showed the demographic features of 157 patients who qualified to receive IV rTPA for thrombolysis from 10 institutions in the Philippines. Majority were males, with a mean age of 60 years. The common risk factors identified were hypertension, diabetes mellitus and atrial fibrillation. Symptomatic and asymptomatic intracranial hemorrhage was noted in 19 (12.1%) and 39 (24.8%) respectively. The in-hospital mortality rate was 23 (14.6%) while death occurred in 5 (3.7%) within 3 months after discharge. Upon discharge 69 (51.1%) are independent with mRS 0-2 while 95 (73.1%) became independent at 3 months. Diabetes mellitus, high NIHSS on admission and hemorrhagic conversion were shown to be significant determinant for mortality within 3 months.

Table 2: Clinical outcome of the stroke patients

Clinical Outcome	Mean ±SD	n(%)	p-value
NIHSS			
Pre-Thrombolysis treatment	12.7±6.20		<0.001*
24 hour post treatment	9.9±8.49		
Mortality rate			
In-hospital		23 (14.6)	
Within 3 months after discharge		5 (3.7)	
MRS – Independent			
On discharge		69 (51.1)	<0.001***
Within 3 months after discharge		95 (73.1)	

Statistical test- *paired t-test; ***McNemar test

Table 3: Univariate and multivariate analysis of the association between the different variables and mortality withinthree months post thrombolysis treatment

Predictor Variables	Adjusted Odds Ratio		p-value*	Adjusted Odds Ratio		p-value*
	Estimate	95% CI		Estimate	95% CI	
Age (years)	1.03	0.98-1.08	0.234	-	-	-
Sex, Male	2.12	0.54-8.32	0.282	-	-	-
Hypertension	0.67	0.67-0.16	0.575	-	-	-
Atrial Fibrillation	0.66	0.15-2.91	0.582	-	-	-
Previous history of stroke	1.33	0.33-5.45	0.690	-	-	-
Coronary artery disease	1.68	0.31-9.18	0.551	-	-	-
Dyslipidemia	0.08	0.01-1.33	0.077	-	-	-
Diabetes mellitus	2.61	0.74-9.16	0.135	3.10	1.05-9.19	0.041
Smoker	0.50	0.11-2.33	0.379	-	-	-
Alcoholic	0.70	0.14-3.52	0.664	-	-	-
NIHSS on admission	1.18	1.07-1.31	0.001	1.16	1.06-1.27	0.002
Door to thrombombolysis (minutes)	1.00	0.99-1.02	0.456	-	-	-
Symptomatic hemorrhagic transformation	24.37	6.29-94.41	<0.001	20.77	5.73-75.20	<0.001

Statistical test - *logistic Regression

To date there is still limited data on thrombolysis in Asia especially in the Southeast Asian region. In 2006 the first single center prospective published paper on thrombolysis in the region came from Thailand.[18]A total of 34 (2.1%) cases received IV rTPA out of 1624 acute ischemic stroke. In-hospital mortality due to intracerebral hemorrhage was seen in 11.8% of thrombolyzed patients. Symptomatic brain hemorrhage was seen 5.9% and there was one death. This is in contrast to our data where there is a higher proportion of symptomatic hemorrhage with our patients. Unfortunately the mRS was not reported in that paper.

Data regarding thrombolysis in Asia has been reported.[19]This is a systematic review of thrombolysis experience in 9 Asian countries. A total of 18 publications satisfied the inclusion criteria set by the authors. There were 9300 patients analyzed in this study. The low dose of IV rTPA was compared with the standard dose as to functional outcome and symptomatic hemorrhage. There was no significant difference between the low and standard dose of rTPA in this systematic

Table 4. Comparison of Dosage: 0.6mg/kg versus 0.9mg/kg

Dose	Number of patient (N=157)	Symptomatic Hemorrhagic Transformation	Mortality	mRS 0-2 at 90 days	mRS 3-5 at 90 days
0.6mg/kg	60 (38.21%)	8 (10%)	10 (16.6%)	45 (75%)	7 (11.66%)
0.9mg/kg	97 (61.77%)	11 (11.34%)	18 (18.55%)	53 (54.53%)	27 (27.83%)

Table 5: Comparative data with SITS-MOST and Cochrane Collaboration

	Philippine experience	SITS-MOST	Cochrane Collaboration
Independent at 3 months (mRS 0-2)	73.1%	54.8%	59.7%
Dependent (mRS 3-5)	8.8%	45.2%	40.3%
Mortality within 3 months	19.3%	11.3%	19%
Symptomatic hemorrhage	12.1%	1.7%	7.3%

review. Our data seem to be consistent with this report of thrombolysis experience in the Asian region more so in the three ASEAN countries included.

Our timelines from symptom-to-door to door-to-needle time based on the American heart Association guidelines for acute ischemic stroke are significantly delayed. Among all the timelines recorded, pre-hospital or stroke-onset to door time show the significant delay prior to thrombolysis. The difficulty in transporting patients to hospital, poor recognition of stroke in the community and referral to stroke-ready hospital could be the reasons for this delay

We compared our experience to a large clinical trial and a meta-analysis in assessing the safety and efficacy of tPA in other countries which are mostly Caucasians eg, Cochrane Collaboration project[16] and SITS-MOST[17]. Comparing our experience, we had a higher proportion of independent patients compared to the two other studies. Intracerebral hemorrhage incidence in the SITS-MOST Study was lower than our experience but somewhat similar with Cochrane Collaboration study on IV thrombolysis. The dependent patients were more frequent in both SITS-MOST and Cochrane collaboration compared to our experience. The results of our study is consistent with the world-wide experience of tPA as to safety and efficacy which has been observed in randomized clinical trials. In a recently concluded randomized trial, comparing 0.6mg versus 0.9mg rTPA for noninferiority study, it has been showed that low dose compared to standard dose tPA did not show any significant difference. Additionally, there was fewer symptomatic intracerebral hemorrhage with low dose tPA regimen.[20]

Our study was also designed to measure the safety and efficacy of tPA among Filipinos. The rate of symptomatic hemorrhage (12%) is higher than among other landmark studies in tPA. Diabetes mellitus or/and with higher NIHSS were associated with symptomatic hemorrhage. These findings are similar with other studies confirming hyperglycemia and diabetes to be associated with increased risk of sICH.[21] Additional exclusion criteria such as presence of diabetes and NIHSS score of 25> are being recommended to avoid symptomatic hemorrhage among for patients receiving rTPA between 3 to 4 ½ hours.[22]

Our study has limitations. First, it is a retrospective study, where data are based mainly on chart review. Second, it involved multiple institutions across the country where some centers follow the international guidelines in utilizing tPA, while in other institutions the stroke services are not in place, which may have added to the delay in the rTPA administration. Third, one center utilized sonothrombolysis where recanalization rate has shown to be more enhanced.[23]Lastly, doses of tPA used in this study varies among centers. These factors may have contributed to the non-uniformity of data.

Despite some limitations of our study, we hope that it would promote and encourage other hospitals across the country to utilize tPA as a standard of care for acute ischemic stroke patients to achieve good outcome stroke patients.

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DISCLOSURE

Conflict of interest: None

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