The Challenges and Clinical Outcomes of Intravenous Recombinant Tissue Plasminogen activator (R-TPA) Administration in a Third World Tertiary Government Hospital in the Philippines

ABSTRACT

BACKGROUND: Stroke is the second most common cause of mortality worldwide and in the Philippines. Intravenous Recombinant Tissue Plasminogen activator(R-TPA), which is provided for free in selected government hospitals, lyses cerebral arterial and venous thrombosis. It is given within a window period of 3 to 4.5 hours from stroke onset. A descriptive, retrospective and prospective analysis is needed to identify the challenges and outcomes in our institution. **OBJECTIVES**: To determine the clinical profile, treatment outcomes and door-to-needle time of acute ischemic stroke patients given intravenous RTPA in our institution (Quirino Memorial Medical Center) from August 2016 to March 2017. **MATERIALS AND METHODS**: From a total of 547 ischemic stroke patients admitted from August 2016 to March 2017, there were 7 patients who underwent Intravenous RTPA. Clinical data was collected through the hospital database. Outpatient follow up was done to assess long term outcome. **RESULTS**: Patients' mean age was 58 years, most were males. Hypertension, smoking and alcohol use were present in all patients. Average NIHSS score upon admission was 7. The average time from stroke onset to admission was 137 minutes, door-to-imaging time and ictus-to-needle time was 17 and 85 minutes, respectively. Length of stay at the emergency room varied. Most patients had improved NIHSS scores and 1 had hemorrhagic conversion. Improved Modified Rankin Scale (MRS) 1 month post-RTPA was also seen, albeit not statistically significant. **CONCLUSION**: Most patients who underwent thrombolysis had improved outcome. However, there was note of delay in drug administration due to laboratory factors and lack of monitored beds.

INTRODUCTION

Stroke ranks second as the leading cause of mortality and is included in the top causes of morbidity worldwide [2, 5, 6]. It also remains as one of the leading causes of death in middle income countries. [5,7]

An estimate of 33 million strokes occur globally and there were 5.8 million mortalities from stroke in 2010. [4] The disease burden is expected to rank fourth by 2020. [5] In the Philippines, stroke is ranked second as the leading cause of mortality, after cardiovascular disease and ranks fifth in disease burden.[2]

The administration of Intravenous Recombinant Tissue Plasminogen Activator (R-TPA) is an ideal treatment for patients with acute ischemic stroke. This medication has been proven to be effective when given within the golden period of 3 to 4.5 hours from stroke onset. However, earlier door to needle time has been shown to have better outcome. [1,2,3,4,5,6,7,8,9,10] Most Asian countries can utilize intravenous thrombolysis for acute stroke management. [1] However, the rate of thrombolysis for acute ischemic stroke remains a challenge in developing countries. [1,4,5,6,7,8] In a survey done in 2012, Japan had the highest rate of patients administered intravenous thrombolysis in Asia.[1] The major obstructions in the administration of intravenous thrombolysis are: a limited therapeutic window, lack of public awareness, cost of the drug, lack of immediate transportation to the hospital and lack of access to neuroimaging and specialized facilities for acute stroke care.[1, 6, 7, 9] These challenges are all common to developing countries, including the Philippines. Nationally, there are only thirty-three acute stroke units, which are vital in maximizing therapeutic outcomes in stroke. Of these, almost half are located in Metro Manila. [2]. Clinical data regarding stroke outcomes after administration of intravenous thrombolysis and door to needle time in local tertiary government hospitals is still lacking. The researchers aim to identify the clinical profile and outcomes of the stroke patients who were admitted in a tertiary Philippine government hospital and were given intravenous thrombolysis. We also aim to identify the door to needle time and to determine the factors that may cause delay.

METHODOLOGY

This is a retrospective, prospective and descriptive study, which involves a total of 7 acute ischemic stroke patients who were admitted at a local government hospital from August 2016 to March 2017. During this time frame, these patients qualified to receive intravenous thrombolysis based on the guidelines set by the Stroke Society of the Philippines. The eligibility of patient selection for intravenous RTPA, including the absolute and relative contraindications, route, dose of intravenous RTPA administration, sequence of events during intravenous RTPA administration, blood pressure control and management of intracerebral hemorrhage following thrombolytic therapy were based on the latest guidelines given by the Stroke Society of the Philippines.

The retrospective arm of this study includes hospital data of the admitted patients, which were collected through chart and records review. Data describing the immediate intravenous RTPA outcome by using the National Institute of Health Stroke Scale (NIHSS), door to needle time, clinical, radiologic and laboratory profile were gathered and analyzed. Descriptive statistics were used to demonstrate the profile of these patients which include the stroke onset, type of stroke, location and laterality of stroke, NIHSS and Modified Rankin Scale (MRS) scores upon admission, NIHSS 24 hours post intravenous RTPA, NIHSS 3 days post intravenous RTPA, NIHSS 7 days post intravenous RTPA, NIHSS upon discharge, presence of concomitant metabolic factors and comorbidities such as heart disease, hypertension and diabetes mellitus type 2, presence of lifestyle factors such as illicit drug use, smoking and alcohol consumption. The incidence of hemorrhagic conversion post intravenous thrombolysis was also

described. The prospective arm of this study assessed the Modified Rankin score of all patients who were given intravenous thrombolysis one month post-discharge, upon OPD follow up.

The confidentiality and privacy of the patients is highly respected. Patient identity is kept confidential and not divulged in any part of the manuscript. Consent was obtained and each patient was given a corresponding “respondent number code” during the encoding of the data. The results of this manuscript include the summary of the data .

A total of 547 patients were diagnosed with ischemic infarctions, regardless of its chronicity and etiology (August 2016: 61, September 2016: 65, October 2016: 81, November 2016: 86, December 2016: 73, January 2017: 74, February 2017: 67, March 2017: 40).

RESULT

Of these, seven acute ischemic stroke patients admitted at a tertiary government hospital last August 2016 to March 2017 were deemed eligible for and underwent intravenous thrombolysis via administration of RTPA.

The following were recorded:

1. Clinical profile
2. Risk factors
3. MRS upon admission

4. NIHSS upon the following time frames: on admission, immediately post RTPA, 1 hour post RTPA, 1 day post RTPA, 3 days post RTPA, 7 days post RTPA and upon discharge
5. Door to needle time
6. Time from ictus to admission
7. Ictus to needle time
8. Complications and incidence of hemorrhagic conversion

Among the 7 patients who were given RTPA, there were 6 (85.7%) males and 1 (14.28%) female with an age range of 48 to 80 years old (mean: 58.2, median: 52). All are right handed. Identified risk factors for stroke are as follows: hypertension (100%), diabetes mellitus type 2 (57%), dyslipidemia (28.5%), hyperuricemia (28.5%), history of previous stroke (28.5%), heart disease (congestive heart failure present in 28.5%), history of illicit drug use (28.5%), smoking history (100%) and history of alcohol beverage intake (100%). Other comorbidities include history of treated pulmonary tuberculosis present in 1 patient (14.28%). Only 3 had and are compliant with maintenance medications. Imaging findings of the patients were recorded during the course of the admission.

Table 1. Clinical profile, risk factors and comorbidities of acute ischemic stroke patients given intravenous RTPA.

Patient Number	Age	Gender	Handedness	HTN	DM	Dyslipidemia	Hyperuricemia	Previous stroke	Heart disease	Illicit drug use	Smoking	Alcohol	Other comorbidities	Maintenance medications
1	52	M	Right	+	+	+	-	+	-	-	+	+	-	+ Losartan 50mg once a day
2	51	M	Right	+	+	+	+	+	-	+	+	+	-	-
3	65	M	Right	+	+	-	-	-	-	-	+	+	-	-
4	50	M	Right	+	-	-	-	-	+	-	+	+	-	+ Losartan 50mg once a day
5	80	F	Right	+	-	-	-	-	-	-	+	+	-	-
6	48	M	Right	+	-	-	+	-	+	+	+	+	+	-
7	62	M	Right	+	+	-	-	-	-	-	+	+	-	+ Losartan 50mg once a day

Table 2. Imaging Findings of the patients

Patient Number	Cranial CT scan results
1	Prior to RTPA: acute infarct left lentiform nucleus and external capsule, Post RTPA: acute hematoma 13.7cc left posterior lentiform nucleus and external capsule with minimal subfalcine herniation with rightward midline shift 2.4mm
2	Subtle hypodensities in the right fronto-parietal lobes, consider hyperacute infarct, old lacunar infarcts, anterior limb of right internal capsule, right lentiform nucleus and right paramedian pons, old infarct, right cerebellar hemisphere
3	Subtle patch of hypodense changes in the left frontal subcortical white matter, to consider hyperacute infarct; chronic lacunar infarct right lentiform nucleus
4	No evidence of acute infarction
5	Acute infarct, right posterior frontal lobe and right parietal lobe, acute ischemic infarction/microvascular ischemic changes right posterior lentiform nucleus and right fronto-parieto-occipital periventricular white matter
6	Upon admission: acute infarction left pons and right thalamus, chronic lacunar infarct left frontal periventricular white matter, Repeat CT scan 3/5/17: small hypodensity in the left paramedian pons, which may represent lacunar infarction, patchy hypodensities in the periventricular white matter of both fronto-parietal lobes, denoting microvascular ischemic changes, CT angiogram: No evidence of aneurysm or vascular malformation, small appearing left anterior cerebral, posterior cerebral and both posterior communicating arteries mat be due to vasopsasm or hypoplasia
7	No evidence of acute infarction or hematoma

Initial stroke presentations include right arm weakness (28.5%), left arm weakness (28.5%), dysarthria (14.28%), dizziness (14.28%) and left facial asymmetry (14.28%). The range of the NIHSS upon admission was 5-9 (mean: 7, median: 7) and the MRS

upon admission was 2-4 (mean: 2.7, median: 3). The laterality of the stroke were mostly right sided infarcts (71.4%).

Table 3. Initial stroke presentations, NIHSS and MRS upon admission and Stroke Laterality.

Patient Number	Clinical presentation	NIHSS upon admission	MRS upon admission	Stroke Laterality
1	Right sided weakness	5	2	Left
2	Dysarthria	7	3	Right
3	Right sided weakness	6	2	Left
4	Left sided weakness	7	3	Right
5	Left Upper extremity weakness	9	3	Right
6	Left Facial Asymmetry	7	2	Right
7	Dizziness	8	4	Right

The timing of RTPA was also described. The ictus to needle time is 1 hour and 40 minutes up to 4 hours and 8 minutes (average: 185 minutes or 3 hours and 5 minutes). Ictus time to admission is 1hour to 3 hours and 15 minutes (average: 2 hours and 17 minutes). The door to needle time varied in patient one as he was admitted directly to the medical ICU with cranial CT scan and laboratory tests done outside our institution. Among the other 6 patients, they had an average of 58 minutes with a range of 25

minutes to 1 hour and 38 minutes. The main cause of delay is due to the lack of immediate availability of the laboratory results arising from technical issues in the Pathology Department.

The length of stay at the emergency room (ER) differs for each patient: patient one was directly admitted to the medical ICU; patient two stayed at the ER for 1 hour and 38 minutes, due to multiple factors: 1. The patient was not immediately referred to the brain attack team 2. The patient was in a wheelchair and there was no available bed in the emergency room 3. The medical ICU and neurology ward were full at that time; patient six stayed at the ER for 4 hours but was given RTPA at the ER with an available ER bed at that time; lastly, patients three, four, five and seven stayed at the ER for 5-10 minutes and were immediately admitted to the Medical ICU or Ward.

The Door to CT scan time was 5 to 27 minutes (average: 10 minute) and the waiting time for the release of laboratory results was 17 minutes to 92 minutes (Average: 52 minutes).

Table 4. Timing of RTPA administration, ictus to needle time, ictus time to admission and door to needle time. Length of ER stay. Processing time of laboratory results. Door to CT scan time.

Patient Number	Ictus to needle time	Ictus upon admission	Door to needle time	Length of ER Stay	Processing Time of Laboratory Findings	Door to CT scan time
1	3 hours and 15 minutes	3 hours and 15 minutes	Upon admission	Direct admission	N/A	N/A
2	4 hours and 8	2 hours and 30	98 minutes	1 hour and 38 minutes	92 minutes	27 minutes

	minutes	**minutes**				
3	**3 hours and 8 minutes**	**2 hours**	**68 minutes**	**5 minutes**	**64 minutes**	**8 minutes**
4	**2 hours and 55 minutes**	**2 hours and 30 minutes**	**25 minutes**	**5 minutes**	**17 minutes**	**10 minutes**
5	**3 hours and 14 minutes**	**2 hours**	**74 minutes**	**10 minutes**	**68 minutes**	**5 minutes**
6	**2 hours and 44 minutes**	**2 hours**	**44 minutes**	**4 hours**	**37 minutes**	**7 minutes**
7	**1 hour and 40 minutes**	**1 hour**	**40 minutes**	**5 minutes**	**35 Minutes**	**5 minutes**

After RTPA administration, 5 of these patients given RTPA had improved NIHSS, while 1 developed hemorrhagic conversion and another developed complications not related to hemorrhagic conversion. In general, the patients who underwent thrombolysis had improved outcomes based on the NIHSS. The average NIHSS 1 hour post RTPA is 5.57 (range: 4-7), after 1 day 6.5 (range: 3-11), after 3 days 5.28 (range: 1-11), after 7 days 5.2 (range: 1-8) and upon discharge 4.7 (range: 1-8). The mean improvement in NIHSS scores post RTPA 1 hour, 1 day, 3 days, 7 days and upon discharge is 1.4, 0.4, 1.7, 1.8 and 2.2 respectively. Patients were followed up at the outpatient department 1 month after discharge. Results showed that there was a mean improvement of 1.25 in the Modified Rankin Scale after 1 month post administration of intravenous RTPA. However, the improvement in scores was not statistically significant. 3 out of 7 patients who were given RTPA were lost to follow up. The reason for this could be the distance

from their home to the hospital, particularly two patients who are from the provinces, namely Zamboanga Del Norte and Pampanga.

Table 5. NIHSS outcome post RTPA 1 hour, 1 day, 3 days, 7 days and upon discharge. Modified Rankin Scale scores upon admission and 1 month post RTPA administration.

Patient Number	NIHSS 1 hour post RTPA	NIHSS 1 day post RTPA	NIHSS 3 days post RTPA	NIHSS 7 days post RTPA	NIHSS upon discharge	Hemorrhagic conversion during RTPA administration	MRS upon admission	MRS 1 month after discharge
1	5	11	9	8	8	+	2	Lost to follow up
2	7	4	4	4	4	-	3	Lost to follow up
3	4	5	3	N/A	3	-	2	1
4	7	3	1	1	1	-	3	1
5	7	8	5	5	5	-	3	2
6	5	11	11	8	8	-	2	2
7	4	4	4	N/A	4	-	4	Lost to Follow up

DISCUSSION

Stroke leads to long term disability and mortality.[2,4] Fifteen million individuals suffer from stroke yearly. Thirty-three percent of stroke patients die and another thirty-three percent suffer permanent disability, which leads to a chronic burden on their families and society. Globally, 3 million women and 2.5 million men die from stroke annually. However, the incidence of cerebrovascular accidents is decreasing in developed countries, as a result of better blood pressure control. The stroke burden is estimated to rise from 38 million Disability-Adjusted Life Year (DALY) in 1990 to 61 million DALYs in 2020 globally.[11]

Stroke in developing countries continues to rise. [5,7,11] It is the most common cause of death and third leading cause of disease burden in middle income countries. Developing countries account for eighty percent of all stroke mortalities globally.[5] The Global Burden of Disease study highlighted that there was a two-thirds increase in the rate of incidence and prevalence of stroke in Asia.[1]

In the Philippines, the age-standardized mortality for stroke is 82.8 per 100,000 person-years where it is the second leading cause of death and ranks fifth with greatest disease burden.[2] In our country, stroke has a prevalence rate of 0.9% of which 70% are ischemic infarctions, while hemorrhagic infarctions would comprise 30%. [12] As of 2014, the neurologist to patient ratio is 1:320,000-330,000 and 67% of these neurologists practice in the urban region.[2,12] The availability of imaging modalities such as computerized tomography (CT) and Magnetic Resonance Imaging (MRI) remains scarce. For every 1 million people, there is only 1.16 (CT) scans and 0.33 (MRI) units available.[2]

Risk factors for stroke include modifiable and non-modifiable conditions. Increasing age and gender are non-modifiable stroke risk factors. Most stroke patients are 60 years old and above and have a male predominance in both ischemic and hemorrhagic stroke.[13] In the Asian population, men also have a higher incidence of stroke compared to Asian women although women have poorer outcomes. These are due to the differences in immunological factors, hormonal changes, changes before, during and after pregnancy which have a major impact on the type of stroke and its outcome.[1] Systemic hypertension remains to be the most significant modifiable risk factor for stroke.[1,2,13] Other modifiable risk factors would include diabetes mellitus, dyslipidemia, cigarette smoking, excessive alcohol intake, cardiac risk factors, extracranial and intracranial carotid stenosis, peripheral arterial diseases, physical inactivity and obesity.[1,,2,13] It is also important to note that nutritional imbalance is included among the modifiable stroke risk factors.[2] The age adjusted prevalence of hypertension, diabetes mellitus, dyslipidemia, smoking and obesity is 20.6%, 6.0%, 72%, 31% and 4.9% respectively.[12] Drug abuse is a common etiologic factor of stroke in the young. This increases the risk of hemorrhagic and ischemic infarctions. Illicit drug use of amphetamine and cocaine is most associated with stroke.[17] Modifiable and non modifiable risk factors for stroke are present in our patients e.g. old age, hypertension, diabetes, heart disease, dyslipidemia, alcohol intake, smoking and illicit drug use.

Evidence-based treatment shows that Intravenous thrombolysis by using RTPA proves to be effective in the management of acute ischemic stroke patients.[1,2,3,5,7,9,14]

Intravenous RTPA is the only thrombolytic drug that is approved for acute ischemic stroke treatment.[1] Intravenous thrombolysis for acute ischemic stroke management is available in the majority of Asian countries and is standard of treatment in the region. However, it has been shown to be less effective in patients with proximal occlusions of the major cerebral arteries, which comprise more than one-third of the anterior circulation stroke.[1] Several trials have shown the effectiveness of RTPA treatment. In the National Institute of Neurological Disorders and Stroke (NINDS) t-PA trial, it showed that patients given intravenous thrombolysis were 30% more likely to have minimal or resolution of disability at 3 months.[2] The Japanese Alteplase Clinical Trial (J-ACT) showed 36.9% improvement in MRS scoring of 0-1 at 3 months.[2] In our study, post intravenous RTPA administered patients have improvement in the MRS scores by 1 point after 1 month, however this is not statistically significant. There was also noted improvement, albeit not statistically significant, in the mean NIHSS scores in most of the patients. The European Australasian Cooperative Acute Stroke Study (ECAS III) revealed that 52.4% of patients had significant improvement at 3 months post RTPA compared to placebo which is 45.2%.[2] The Third International Stroke Trial (IST III) also showed benefit of 37% compared to placebo (35%) at 6 months, for patients given IVRTPA.[2] However, in our institution, further monitoring of the patient's MRS was not done more than 1 month after their initial OPD follow up. This is due to financial and geographical factors.

Appropriate timing of the administration of intravenous thrombolysis is a key factor in good clinical outcome of acute ischemic stroke patients. The door to needle times for patients receiving intravenous RTPA differs among regions in the world. The Safe

Implementation of Thrombolysis in Stroke Monitoring Study (STIS-MOST) which included patients in Europe, has a door to needle time of 68 minutes. The door to needle time in Canada as stated by the Registry of the Canadian Stroke Network (RCSN) is 80 minutes, while in America, the door to needle time averaged 90 minutes. In China, the door to needle time is 116 minutes.[6] The stroke onset to needle times for patients have been discussed by SIT-MOST, RCSN and China National Stroke Registry (CNSR) which is 140 minutes, 161 minutes and 180 minutes respectively.[6] The comparison of door to imaging and imaging to needle times has been recorded by the following studies: in RCSN, the door to imaging time is 31 minutes and imaging to needle time is 50 minutes, in the United States, the door to imaging and imaging to needle time is 20 minutes and 65 minutes respectively, while China, which has the longest door to needle time, has a door to imaging time of 30 minutes, similar to Canada, but has an imaging to needle time of 90 minutes.[6]

In developing countries like India, as reported by Padma Et. Al 2007, the mean door to imaging time is 24 minutes and door to intravenous thrombolysis time is 26.8 minutes (range 25-67 minutes). It reported that 65% of the patients had significantly improved NIHSS score at 48 hours (mean change of 10) and at 1 month 79% had improved Barthel Index (mean change 45%). The study concluded that intravenous thrombolysis is safe in selected patients with acute ischemic stroke even with the absence of coagulation studies.[15] A prospective case series done in Asia as reported by Suwanela et. Al in 2006, showed a mean door to needle time of 72.6 minutes (range 20-150 minutes). Major neurologic improvement was observed in 50% of patients given intravenous RTPA at 24 hours.[16] Ghanderi in 2010 reported that stroke patients in

Gambia and Ethiopia reached the hospital 8 hours and 13.5 hours post stroke symptom onset, respectively. In Iran, 8% of stroke patients reached the hospital within 3 hours of stroke onset. While in India it was reported that only14.7% of stroke patients were able to reach the hospital within 3 hours.[7]

Currently, there are no local published data regarding the door to needle time in tertiary government hospitals in the Philippines. In our institution, the average door to needle time is 185 minutes and the average time from ictus to admission is 2 hours and 17 minutes. This is comparable to the international data of developing countries.

Ghanderi 2010 also described the barriers of thrombolysis therapy in developing countries. These include prehospital barriers, financial constraint and lack of infrastructure.[7] Prehospital barriers of thrombolytic therapy includes inability of the family members, the public and other health care workers to recognize the signs of stroke. We have instituted activities to educate the lay people as well as barangay health workers in order that stroke awareness may be raised.

Patterns of health behavior are also important. Acute stroke patients in Bolivia do not immediately seek help in the hospital, and other developing countries like Iran are lacking in ambulance services.[7] Financial constraints is one of the main factors for the lack of RTPA usage. Most health insurance companies in developing countries do not cover the cost of RTPA for stroke patients.[7] The lack of CT scan and MRI imaging in developing countries imposes a huge hindrance in giving intravenous RTPA to patients. In the Philippines there are only 1.16 CT scans and 0.33 MRI units available for every 1 million patients.[2] Challenges in our institution include the occasional malfunction of CT scan imaging and laboratory/diagnostic modalities (e.g. PT/PTT), the lack of continuous

availability of RTPA medications, lack of manpower and inadequate ward/ICU vacancies. These factors influenced the duration of door to needle time in our study. Our average door to needle time is 58 minutes. The major cause of delay is waiting for the release of laboratory results which has a mean waiting time of 52 minutes. All of these must be addressed to hasten the administration of thrombolytic therapy.

CONCLUSION

There was improved clinical outcome in our patients after the administration of Intravenous RTPA. This, however, is not statistically significant due to the small number of patients included in this study. Intravenous RTPA administration remains to be a challenge locally especially in government hospitals. As described in Iran and India, only 8% and 14.7% of their total stroke patients were able to arrive at the ER in less than 3 hours from symptom onset. In our institution the average time from ictus to admission was 2 hours and 17 minutes. Patient and public health education regarding the severity of stroke and the urgency to seek medical care is needed to break down the barriers delaying ictus to needle time.

In comparison to other studies, the average onset to needle time of our institution (185 minutes) was comparable to that of the Chinese National Stroke Registry (180 minutes) but lags behind the SITS-MOST (140 minutes) and RCSN (161 minutes) trials. One restriction in our institution was failure of personnel to urgently respond to the rapid processing of the diagnostic and laboratory examinations of brain attack patients. Technical malfunctions, lack of hospital beds, lack of hospital manpower pose a challenge in the Philippines. Methods which may be used to compensate for technical and manpower insufficiencies include: 1. Rapid and accurate triaging of stroke patients which will significantly decrease the ER waiting

time and the door to imaging time; 2. Direct admission of brain attack patients to the MICU or ward, and 3. The administration of RTPA at the ER level if with an available monitored ER bed, with adequate supervision of the nurses and residents.

Understandably, hospitals differ in the availability of equipment and manpower expertise, hence it is important to formulate a customized pathway for the administration of intravenous RTPA in government institutions in the Philippines. Furthermore, a follow-up study with a larger patient population may help us ascertain if such administration of IVRTPA will provide statistically significant improvement.

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