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SPECIAL REPORT

Utilization and outcomes with low dose tissue plasminogen activator as intravenous thrombolytic therapy for ischaemic stroke at Aga Khan University Hospital, Karachi: a retrospective analysis

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Abstract

Objectives: To determine the utilisation of intravenous tissue plasminogen activator at a certain dose for ischaemic stroke thrombolysis and to compare the outcomes with those of a different dosage mentioned in literature.

Methods: The retrospective study was conducted at the Aga Khan University Hospital, Karachi, and comprised medical records from January, 2007, to October, 2016, of all patients having received intravenous tissue plasminogen activator for ischaemic stroke thrombolysis. Primary safety outcome variables included symptomatic intracerebral haemorrhage after the start of treatment (0.6mg/kg) and death within three months as per the modified Rankin scale 6. Secondary efficacy outcome variable was functional independence as per modified Rankin scale 0-2 at three months. The outcomes were compared with those mentioned in literature with a dose of 0.9mg/kg.

Results: Of the 79 patients, 52 (66%) were male and 27 (34 %) were female. Median pre-treatment tissue plasminogen activator score was 12 (interquartile range: 8-15). Overall utilisation of t-PA remained at 1.7%. Symptomatic intracerebral haemorrhage was not seen in our cohort while it was seen in 107 (1.7%) patients at the higher dose. Using another definition, it was seen in 3 (3.8%) patients versus 468 (7.3%) patients at the higher dose. Functional independence was seen in 40 (50.6%) patients at three months compared to 3362 (54.8%) patients at the higher dose.

Conclusion: Low-dose intravenous thrombolytic therapy for ischaemic stroke patients was found to be safe and efficacious, and yielded comparable results with those obtained at a higher dose.

Keywords: Ischemic stroke, IV thrombolysis, Low dose, Asians. (JPMA 69: 1705; 2019).

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Introduction

For the management of acute stroke, a major breakthrough came in 1996 when the National Institute of Neurological Disorder (NINDS) trial proved that treatment with intravenous (IV) tissue plasminogen activator (t-PA) within three hours of the onset of ischaemic stroke improved clinical outcome at three months.[1] Since then, its use has been expanding, particularly in the developed countries. In contrast, developing countries have displayed limited progress in the management of patients with acute stroke despite increasing incidence of stroke and high stroke mortality rates that account for over two-thirds of stroke deaths worldwide.[2] There are only two longitudinal studies on the utilisation and outcome of thrombolytic therapy for acute stroke in Pakistan to date.[3,4] Both studies had small sample sizes (21 and 13 patients respectively) along with different t-PA dosage regimens and did not use the established outcome parameters. The paucity of literature on the safety and efficacy of intravenous t-PA, especially in the Pakistani population, necessitates further investigation. The current study was planned to determine the utilisation and outcomes with low-dose t-PA for ischaemic stroke thrombolysis at our hospital, and to compare the results with those reported in the safe implementation of thrombolysis in stroke monitoring study (SITS-MOST).[5]

Methods and Results

The retrospective study was conducted at the Aga Khan University Hospital (AKUH), Karachi, and comprised medical records from January, 2007, to October, 2016, of all patients having received intravenous t-PA for ischaemic

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stroke thrombolysis.

After taking permission from the institutional ethics committee, cases were identified through the International Classification of Disease (ICD-9) coding system[6] maintained at the AKUH. Primary safety outcome variables were symptomatic intracerebral haemorrhage (sICH) after start of thrombolysis and mortality within 3 months as per the modified Rankin Scale (mRS 6).[7] Secondary efficacy outcome variable was functional independence (mRS 0-2) at 3 months. The sICH, as per SITS-MOST definition, was defined as intracerebral haemorrhage (ICH) (parenchymatous haemorrhage type 2) at post-treatment scan combined with neurological deterioration leading to an increase of 4 points or more on the National Institute of Health Stroke Scale (NIHSS).[8] ICH, as per the Cochrane definition,[9] was defined as intracerebral haemorrhage with any drop on NIHSS. Other clinical variables of interest included asymptomatic ICH (aICH), ICH, bleeding events other than ICH and cerebral oedema (COED) at computed tomography (CT) follow-up after thrombolysis treatment. We also looked at percentage of patients cured (mRS 0), those who had favourable outcomes (mRS 0-1), baseline characteristics of patients with sICH, outcomes in aetiological subgroups / Trial of 'ORG 10172' in Acute Stroke Treatment (TOAST) classification[10] and duration of hospitalisation.

The proportion of ischaemic stroke patients receiving t-PA was calculated and the causes summarised with the associated frequencies. The proportions and 95% confidence intervals (CIs) of patients with ICH and mRS ≤2 as well as mortality (mRS 6) was calculated for all patients receiving t-PA. The frequency and proportion of patients with primary and secondary outcome events, i.e., the incidence of sICH at CT follow-up, mortality and functional independence was compared with SITS-MOST results. ICH was classified on CT scans according to the SITS-MOST definitions.

A total of 80 were identified, but 1(1.25%) case had to be excluded as it did not have post-t-PA scan There was an upward yearly trend towards utilisation of t-PA (Figure 1).

Baseline data, including demographics, risk factors, co-morbids, treatments for other diseases at stroke onset for patients at AKUH and SITS-MOST along with causes and subtypes of stroke and time from symptom onset to t-PA administration were noted at the outset (Table 1).

Among our cases, pre-t-PA median NIHSS of the patients score was 12 (interquartile range [IQR]: 8-15). Of the 79 patients, 19(24%) had haemorrhages on post-treatment imaging scans which had a statistically linear trend with pre-t-PA NIHSS severity category on Cochran-Armitage test of trend (p=0.015). Post-t-PA NIHSS was available for only 9(11.4 %) patients with a median score of 9(IQR: 7-13.5) and a median improvement of 3(IQR: 0-5). NIHSS at discharge was available for only 2(2.5%) patients with

Table-1: Baseline characteristics of patients enrolled in AKUH and SITS-MOST.

	AKU (n=79)	SITS-MOST (n=6483)
Age(years)	62 (54-70)	68 (59-75)
Gender (female)	27 (34.2%)	2581 (39.8%)
Independence (modified Rankin score 0-1) before stroke	79/79 (100%)	5899/6337 (93.1%)
Hypertension	56/79 (70.9%)	3710/6318 (58.7%)
Diabetes Mellitus	24/79(30.4%)	1020/6374 (16.0%)
Ischaemic Heart Disease	19/79 (24.1%)	-
Smoking	16/79 (20.3%)	2643/6114 (43.2%)
Current	11	1474
Previous	5	1169
Antiplatelet	26 (32.9%)	1918/6441 (29.8%)
Antihypertensive	42 (53.2%)	2983/6429 (46.4%)
Blood Glucose (mg/dl)	127.8 (102.6-176.4)	115.2 (100.8-138.6)
Weight (Kg)	70 (61 - 80)	75 (68-85)
Systolic Blood Pressure (mm Hg)	150(130-171)	150 (137-166)
Diastolic Blood Pressure (mm Hg)	81 (70-96)	81 (74-90)
Degree of neurological severity (pre t-PA NIHSS)	12 (8-15)	12 (8-17)
Mild (NIHSS 1-7)	17/79 (21.5%)	1494 (23%)
Moderate (NIHSS 8-14)	39/79 (49.4%)	2409 (37%)
Severe (NIHSS ≥15)	23/79 (29.1%)	2571 (40%)
Previous stroke	5/79(6.3%)	643/6395 (10.1%)
Previous stroke and reduced functional status (mRS>1)	0/79 (0 %)	80/643 (12.4%)
Cause of stroke		
Large vessel disease with substantial carotid stenosis	5 (6.3%)	844 (13%)
Large vessel disease other than substantial carotid stenosis	8 (10.1 %)	1435 (22.1%)
Cardiac origin	41 (51.9%)	2270 (35%)
Lacunar stroke	4 (5.1 %)	535 (8.3%)
Other	15 (19 %)	1171 (18.1%)
Unknown	6 (7.6 %)	228 (3.5%)
Stroke onset to treatment time (min)	165 (135-215)	140 (115-165)
Mean delay between stroke onset and treatment (min)	175 (56)	136 (33)
Treated within 90 min	3 (3.8%)	671 (10.6
Treated within 90 - 120 min	10 (12.7 %)	N/A
Treated within 120-180 min	36 (45.6%)	4276 (66%)
Treated within 180 - 270 min	30 (38%)	N/A
Door-to-needle time (i.e. from entering the facility to receiving treatment with alteplase) (min)	96 (31)	68 (30)

Data are median (IQR), mean (SD), or n (%). AKUS: Aga Khan University Hospital.SITS-MOST: Safe implementation of thrombolysis in stroke monitoring study, t-PA: Tissue plasminogen activator, NIHSS: National Institute of Health Stroke Scale, mRS.

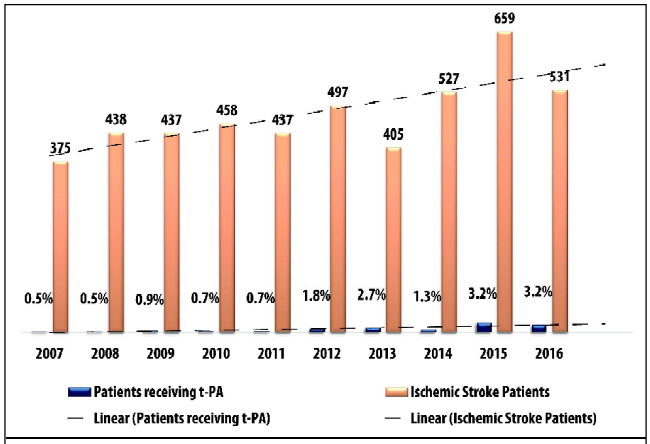

Figure-1: Yearly tissue plasminogen activator (t-PA) utilisation in Ischaemic Stroke at Aga Khan University Hospital (AKUH).

Table-2: : Proportions of patients with symptomatic intracerebral haemorrhage, mortality and independence at 3 months at AKUH and SITS-MOST.

	AKUH Proportion (events/total; 95% CI)	**SITS-MOST** Proportion (events/total; 95% CI)
sICH rates per SITS-MOST*	0 % (0/79)	1.7% (107/6444; 1.4-2.0)
sICH per Cochrane / NINDS definition†	3.8 % (3/79; 1.3 - 10.6)	7.3% (468/6438; 6.7-7.9)
Mortality within 3 months	1.3 % (1/79; 0.2 - 6.8)	11·3% (701/6218; 10.5-12.1)
Independence (modified Rankin score 0-2) at 3 months	50.6 % (40/79; 39.8 - 61.4)	54.8% (3362/6136; 53.5-56.0)

sICH: Symptomatic intracerebral haemorrhage. * Intracerebral haemorrhage (parenchymatous haemorrhage type 2) at post-treatment scan combined with NIHSS drop ≥ 4. †NIHSS drop ≥1 and any haemorrhage.

Table-3: : Types of intracerebral haemorrhages detected by CT after treatment.

	Haemorrhages on any post treatment imaging scans	
	AKUH (n=79)	**SITS-MOST** (n=6352)
No Haemorrhage	60 (75.9 %)	5267 (82.9%)
Haemorrhagic infarct type 1	9(11.4%)	402 (6.3%)
Haemorrhagic infarct type 2	6(7.6%)	297 (4.7%)
Primary intracerebral hemorrhage type 1	3 (3.8 %)	202 (3.2%)
Primary intracerebral haemorrhage type 2	1(1.3%)	184 (2.9%)

AKUS: Aga Khan University Hospital, SITS-MOST: Safe implementation of thrombolysis in stroke monitoring study.

score improvement of 1 and 3. Due to incomplete NIHSS scores they were not included in the overall comparison and results.

AKUH data was compared against SITS-MOST for symptomatic ICH, as defined by the Cochrane and SITS-MOST definition, mortality and independence for activities of daily living (Table 2). The only mortality 1(1.3%) at AKUH was a patient with atherothrombotic stroke according to TOAST classification who had developed post-t-PA symptomatic intracerebral bleed secondary to

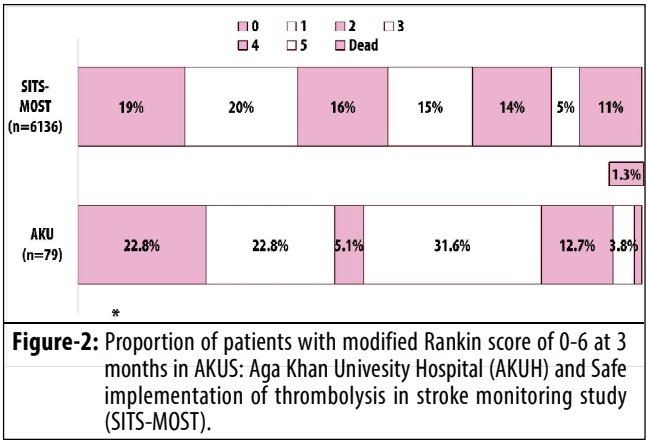

Figure-2: Proportion of patients with modified Rankin score of 0-6 at 3 months in AKUS: Aga Khan Univesity Hospital (AKUH) and Safe implementation of thrombolysis in stroke monitoring study (SITS-MOST).

thrombolytic treatment compared to 701(11.3%) deaths in the SITS-MOST trial, out of which death related to thrombolytic treatment was the outcome in 94(14%) cases.

Also compared was three-month mRS distribution between AKUH and SITS-MOST (Figure 2), and the distribution and types of haemorrhages (Table 3).

The breakup of time from symptom onset to treatment time was found to be a major contributor with a median of 75(IQR: 40-120) minutes. The median length of hospital stay was 4(IQR: 2-5) days.

Discussion

Studies have reported that 15 million people suffer from stroke worldwide each year. Of these, almost five million stroke affected people do not survive, five million are left permanently disabled and five million recover from their symptoms.[11] The estimated annual incidence of stroke in Pakistan is 250/100000, translating to 350,000 new cases every year.[12]

In the past two decades, considerable development in stroke care has been observed. Particularly, mortality and dependence rates in developed countries have been substantially reduced in patients undergoing acute management as well as those who are in rehabilitation and long-term care. Stroke is placed as the fifth major cause of death after years of being the third leading cause of death in the United States,[13] suggesting an improvement in stroke care management and related protective measures.

Currently t-PA is the only approved medical therapy for patients with acute ischaemic stroke. The American Heart Association (AHA) / American Stroke Association (ASA) recommend that t-PA at 0.9mg/kg be instituted within

four-and-a-half hours of symptoms onset for eligible patients.[14] International data on t-PA depicts complete recovery in 39% patients at three months whilst a haemorrhage rate of 7.3 per cent and mortality of 11.3 per cent have been noted as per SITS-MOST definition.[5] A lower dosage (0.6mg/kg) is being used variably in the Asian population citing comparable safety and efficacy profiles compared to the standard dose in Western population.[15]

The safety and efficacy outcomes in our patients were comparable with that of SITS-MOST5. Standard dose (0.9mg /kg) of IV alteplase was being used at AKUH in 2005-07 When 18/1185 (1.5%) acute stroke patients were thrombolysed with fatal ICH seen in 3(14%) patients and non-fatal haemorrhage in 2(10%).[15] This led to a shift in the institutional protocol towards using low-dose (0.6mg/kg) IV alteplase for thrombolysis in ischaemic stroke. When compared with the regional data, a prospective study on 176 stroke patients who received standard dose IV thrombolysis in Dubai[16] reported 12(6.8%) patients developing symptomatic ICH opposed to 0% in the current study. Two-thirds (62.1%) of patients in the earlier study[16] were of South Asian origin. Median NIHSS was 12 (IQR: 9-15) which is similar to our results. Another study from India[17] showed haemorrhagic transformation in 5/54 (8.8%) patients who received standard dose IV thrombolysis. It reported no symptomatic haemorrhage, but the definition used was not been specified.[17] Another study from India[18] reported symptomatic ICH to have occurred in 2/32 (6.25%) patients thrombolysed with standard dose alteplase whereas haemorrhagic conversion was noted in 3/32 (9.3%) patients. Standard dose thrombolysis is being administered at Shifa International hospital, Islamabad, where 13/312 (4.1%) stroke patients received IV t-PA during the first year of its utilisation.[3] None of the patients developed symptomatic ICH, but the definition used was not specified.[3] The Mean NIHSS was 14.85±5.289 and t-PA was not administered in the extended window in any of the patients.[3]

The mRS at three months was not consistently reported in the regional thrombolysis studies.[3,16-18] In one study,[16] mRS at 3 months was available for only 71.176(40%) patients thrombolysed. Independence (mRS 0-2) was reported in 61(85.9%) of these 71 patients.[16] It was noted that majority of the patients who did not attain good functional recovery might have gone back to their home countries and were thus lost to follow-up. Safety outcome data at 3 months (mRS) in our patients was comparable with those reported in Western studies.[5,19,20]

Increased bleeding tendency after exposure to thrombolytic agents has been reported in Asian population as opposed to Western population owing to differences in coagulation and fibrinolytic pathways.[21] The rationale for using low-dose alteplase in ischaemic stroke patients come from Japanese alteplase clinical trial (J-ACT) in which low-dose thrombolysis was found to have comparable efficacy and safety compared with standard-dose thrombolysis in western population.[22] Multiple studies done afterwards to establish an optimal dosing protocol for Asian population have yielded contradictory results which has resulted in variable dosing regimens in different regions and, at times, in different hospitals within the same country.[23] Recently Enhanced Control of Hypertension and Thrombolysis Stroke (ENCHANTED) study, designed to compare the efficacy of 0.6 mg/kg alteplase with 0.9 mg/kg, could not demonstrate non-inferiority between the two doses when assessing disability and death as outcome with no difference between Asians and non-Asians.[24] This contradicts the J-ACT trial and the Asian practice of using low-dose alteplase. However, ordinal analysis of mRS scores did show non-inferiority between the two and revealed decreased mortality but increased disability towards the milder end of mRS in the low-dose group. Furthermore, there was a definitive lower risk of sICH in the low-dose alteplase group. Considering these facts, there is still enough evidence to consider low-dose alteplase therapy.[25] The definite answer to this question, however, requires further well-designed large-scale studies.

The utilization of t-PA remained low (1.7%) in the current study. This trend has been seen across South Asia[3,4,17] compared to Western countries (7%).[26,27] The major reasons identified for this include lack of awareness, infrastructure constraints, safety and non-affordability as expenses are to be borne by patients or their families.[4,23] Due to non-availability of license to import t-PA from the federal Ministry of Health, different hospitals in Pakistan have to acquire t-PA on their own. Alteplase comes in 50mg vials only. It amounts to around US$763 per patient whereas the per capita income in Pakistan is around US$1,56128. Establishing a low-dose thrombolysis regimen, if proven effective, especially in Pakistan as well in underdeveloped parts of Asia, is of paramount

importance as the burden of stroke is expected to rise in the future.[29]

The current study is the largest reported data from a single centre in South Asia regarding safety and efficacy of low-dose thrombolytic therapy in ischaemic stroke patients. Nevertheless, the study is not without limitations as it has a retrospective design, lacks a control arm, and still has a relatively small sample size in the wider context.

In the light of the findings, however, it is recommended that thrombolytic therapy should be offered to all patients with ischemic stroke meeting the inclusion criteria and have no contraindications. Because of increased risk of intracerebral bleed with standard dose (0.9mg/kg) of t-PA in our population and low usage rate, it might be preferable to use low dose (0.6mg/kg). There is a dire need for a large-scale study to establish definitively the efficacy and safety of the two doses in our population. Unnecessary delays and deviation from standard protocols should be avoided and public awareness programmes regarding the management of acute stroke shall be introduced.

Conclusion

Low-dose intravenous thrombolytic therapy for ischaemic stroke patients was found to be safe and efficacious, and yielded comparable results with those SITS-MOST.

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Conflict of Interest: None.
Source of Funding: None.

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