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Intravenous Thrombolysis in Hyperacute Ischemic Stroke: NINS, Bangladesh Experience of First 100 Cases

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Abstract

Background: Intravenous thrombolytic therapy is associated with a significant net reduction of disability after acute ischemic stroke. However, information on the benefit–risk profile of thrombolytic therapy in hyperacute ischemic stroke in Bangladeshi people is unavailable at present. The present study was aimed to share the experiences and to determine the predictors of functional outcome of intravenous thrombolytic therapy in a sample of Bangladeshi patients with hyperacute ischemic stroke.

Methodology: This retrospective cohort study included patients with hyperacute ischemic stroke aged between 18 and 80 years old who received IV rtPA in the first 4.5 h time window from the onset of stroke symptoms in between December 2019 to August 2021. The patients' demographics, baseline characteristics and location of stroke were documented. Stroke severity was assessed at time of admission and 24-h after IV rtPA using NIHSS score. All the data were analyzed and correlated with the mRS at 3-months after receiving IV rtPA.

Results: Among the thrombolysed patients, around half (45%) of them had severe stroke (NIHSS score >9). Mean admission NIHSS score was 9.45 (±4.56) whereas mean NIHSS score at 24-hours rtPA was 5.71 (±5.92). Functional outcome was assessed by mRS score at 3-months with a mean score of 1.94 (±2.2), where good outcome was found in 70% patients. In the study, age <70 years (OR, 0.31; 95% CI, 0.15-0.71; p=0.008), NIHSS Score <10 (OR, 0.06; 95% CI, 0.04-0.52; p=0.001) and door-to-needle time <60 mins (OR, 0.4; 95% CI, 0.09-0.94; p=0.02) were associated with good functional outcome (mRS, 0-2) whereas, door-to-needle time >60 mins (OR, 3.27; 95% CI, 1.06-10.1; p= 0.02) and symptoms onset 3-4.5 hours (OR, 1.58; 95% CI, 1.15- 2.78; p=0.03) were associated with poor functional outcome (mRS, 3-6).

Conclusion: Intravenous thrombolytic therapy improves the overall functional outcome among hyperacute ischemic stroke patients. In patients aged less than 70 years, admission NIHSS score <10, door-to-needle time and onset to needle time could be used as independent predictors of functional outcome.

Keywords: Hyperacute ischemic stroke, IV thrombolysis, Alteplase, NIHSS score, mRS score

Introduction

Stroke is the second most common cause of death and it accounts for 11.0 % of total deaths in 2015 and the fifth leading cause of death in the USA; in addition more than 80.0% strokes are ischemic strokes[1]. Globally, stroke burden on families and society is projected to rise from approximately 38 million disability-adjusted life years (DALYs) in 1990 to 61 million DALYs in 2020 due to population aging and is projected to further rise till 2030[2]. According to the survey on stroke, the prevalence of stroke in Bangladesh is 1.96 per 1000 population[3]. The majority of cases (82.3%) occur in individuals over the age of 40[4].

Intravenous thrombolytic therapy remains the guideline-recommended treatment to improve outcomes after acute ischemic stroke—especially in patients without proximal arterial occlusion—and is associated with low complication rates[5]. Intravenous thrombolytic therapy improves functional outcome at three to six months when given within 4.5 h of ischemic stroke onset[6].

Alteplase is associated with a significant net reduction in death and disability after ischemic stroke despite a small but significant increase in the risk of intracerebral hemorrhage (ICH). The use of alteplase is limited to fewer

than 5% of AIS patients[7]; however, because of the limited therapeutic window, insufficient awareness among public and professionals and undue worries about the risk of ICH[8]. Two observational studies—the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) in Europe[9] and the Canadian Alteplase for Stroke Effectiveness Study (CASES)[10]—both confirmed that rtPA is safe and effective when the treatment protocol is closely followed. However, intracerebral hemorrhage remains the most feared side effect of rtPA[11].

In America and Europe, the current rt-PA dose for acute ischemic stroke is 0.9 mg/kg. In contrast, the optimal dose required for attaining a coronary potency rate of 65% to 80% is 0.5 to 0.75 mg/kg in Japan and China, far lower than in Europe and the United States (approximately 1.25 mg/kg)[12-15] a lower dose (0.6 mg/kg) was used in the Japan Alteplase Clinical Trial (J-ACT)[16]. The safety and efficacy of rt-PA in the J-ACT were comparable to that in the National Institute of Neurological Disorders (NINDS) study[17] low-dose alteplase (0.6 mg/kg) for acute ischemic stroke was approved in Japan in 2005.

Later studies in Japan also confirmed that low-dose therapy has similar outcomes compared with regular-dose therapy in western patients[18, 19]. However, information on the benefit–risk profile in the thrombolytic treatment of hyperacute ischemic stroke in Bangladeshi people is unavailable at present. In view of this, the study was aimed to share the experience as well as to determine the predictors of functional outcome of intravenous thrombolytic therapy in a sample of Bangladeshi patients with hyperacute ischemic stroke.

Methodology

Study Settings and Population

This retrospective cohort study was done in National Institute of Neurosciences and Hospital (NINS & H), Dhaka, Bangladesh. Patients with hyperacute ischemic stroke aged between 18 and 80 years old who received IV rtPA in the first 4.5 h time window from the onset of stroke symptoms were enrolled in the study. Patients received treatment with intravenous thrombolytic therapy (Alteplase) according to the last updated guidelines of American Heart Association and American Stroke Association (AHA/ASA). Patients were enrolled in retrospective manner from stroke registry who were treated between December 2019 and August 2021. Before enrollment, informed written consent was taken and confidentiality was kept.

Study Procedure

We analyzed patients demographic, baseline characteristics, location of stroke lesion based on CT brain, and classified strokes into anterior circulation and posterior circulation ischemic stroke. Stroke severity was assessed at time of admission and 24-h after IV rtPA using NIHSS score and was then categorized into mild stroke (when the NIHSS score was <5; moderate stroke when the NIHSS score was from 5-9), and severe stroke (when the NIHSS score was >9)[20]. Door-to-needle time which was a parameter of efficiency of acute stroke care system was also assessed. It was assessed timing of IV rtPA administration from onset of stroke symptoms which is a possible potential predictor of the functional outcome. Comorbidities (e.g, HTN, IHD, DM, AF) were recorded. All the previous data were analyzed and correlated with the mRS at 3-months after receiving IV rtPA. Patients with mRS score 2 or less were considered to have a good functional outcome and patients with score 3 or more were considered to have poor functional outcome[21]. Post-IV rtPA ICH was defined as any hemorrhage in the brain documented by CT or MRI within 36 h after thrombolysis. ICH was classified into symptomatic (sICH) and asymptomatic ICH and sICH was defined as hemorrhage exceeding 30% in the infarcted area with significant space occupying effect with deterioration in NIHSS score of ≥ 4 points or death[22].

Allocation of Drug

Actilyse 50 mg vial at a dose of 0.6 to 0.9 mg/kg intravenously (10% bolus infused in1 min, the remaining 90% infused over 1 h).

Follow Up and Outcome Measures

Patients were followed up prospectively to assess the

functional outcome at 3 months after IV rtPA using mRS, which was a tool used to assess the functional status of the stroke survivors. The primary outcome of the study was safety, which was assessed by the occurrence of symptomatic intracerebral hemorrhage (sICH) and death within 3 months. The secondary outcome was efficacy, which was measured with functional outcome at 3-months by the modified Rankin Scale (mRS). As the COVID-19 situation was ongoing, follow-ups were done using telephone and social media—whichever was available.

Statistical Analysis

Quantitative data (continuous variables) were expressed as means and median, standard deviation and interquartile range (IQR) where applicable. Qualitative data (categorical variables) were expressed as counts and percentages. Data was analyzed by chi-square test, student's t test, and logistic regression analysis where P value <0.05 were considered statistically significant. Predictive factors were presented in the form of odds ratio with 95% confidence interval (CI). Data was analyzed by IBM SPSS software package version 22.0 (Armonk, NY: IBM Corp).

Results

The study was included total 100 patients; male were 77 (77.0%) and female were 23 (23.0%), age ranged between 30 and 80 years with mean age 53.97 (±12.89) years. Hypertension 60 (60.0%), DM (18.0%) were the most common comorbid risk factor. Two third (61.0%) of the patients reached to the hospital within 3-4.5 hours of symptom onset (onset to needle time) but most of the patients (85.0%) received thrombolysis within 60 mins of admission (door-to-needle time) (table 1).

Hemiparesis (98.0%), speech difficulty (67.0%), and facial deviation (66.0%) were the most common presenting features of the patients. Based on NIHSS score, severity of stroke was categorized into mild, moderate and severe, where 16 (16.0%) patients had mild, 39 (39.0%) moderate and 45 (45.0%) patients had severe stroke. Mean admission NIHSS score was 9.45 (±4.56) whereas mean NIHSS score at 24-hours rtPA was 5.71 (±5.92) and mean ASPECTS score was 9.38 (±1.12). Total 8 (8.0%) patients developed intracerebral hemorrhage following IV rtPA where 5 patients had asymptomatic and 3 patients had symptomatic intracerebral hemorrhage (table 2). Functional outcome was assessed by mRS score at 3-months with a mean score of 1.94 (±2.2). Good (0-2) outcome was found in 70 (70.0%) and poor (3-6) outcome in 30 (30.0%), where 17 (17.0%) patients died (table 3).

In the study, the demographic characteristics like gender and the comorbid risk factors showed no significant association (p>0.05) with the functional outcome. But age <70 years was associated with good functional outcome (OR, 0.31; 95% CI, 0.15-0.71; p=0.008). Also NIHSS Score <10 (OR, 0.06; 95% CI, 0.04-0.52; p=0.001) and door-to-needle time <60 mins (OR, 0.4; 95% CI, 0.09-0.94; p=0.02) were associated with good functional outcome (mRS, 0-2). On the other hand door-to-needle time >60 mins (OR, 3.27; 95% CI, 1.06-10.1; p= 0.02) and onset of symptoms 3-4.5 hours (OR, 1.58; 95% CI, 1.15- 2.78; p=0.03) were associated with poor functional outcome (mRS, 3-6) (table 4).

Discussions

This study has demonstrated that use of intravenous thrombolytic therapy for hyperacute ischemic stroke is associated with better functional and neurological outcomes and significantly reduce the effect of stroke morbidity; this was in agreement with several studies that supported the short- and long-term outcome benefits of IV rtPA like the large third international stroke trial[23] and the systematic review and meta-analysis study of real-world outcomes of hyperacute ischemic stroke treatment with intravenous thrombolysis[24].

This present study showed highly significant correlation between admission NIHSS score and the functional outcome, consequently categorical classification of stroke severity, and 24h after receiving IV rtPA. These correlations were found in the multinomial logistic regression analysis, showing that the NIHSS score <10 was considered to be a strong independent predictor of the functional outcome—its increase was associated with poor functional outcome

and vice versa and this was in agreement with the study conducted by Alejandro et al[25].

This study showed non-significant correlation between hypertension and functional outcome 3-months after receiving IV rtPA, which was similar to several studies which found non-significant correlation between history of hypertension and the functional outcome[26, 27]. On the contrary, there were previous studies which revealed association between presence of hypertension and poor functional outcome 3-months after IV rtPA[28].

This study did not show significant correlations between DM and functional outcome after receiving IV rtPA, which was similar to other studies[29, 30]. This result was contrary to studies which had identified DM as a predictor of poor functional outcome after receiving IV rtPA among stroke patients conducted by Roquer et al[31].

In our study, there was non-significant correlation between post-rtPA ICH (asymptomatic, symptomatic) and functional outcome, which was contrary to majority of studies exploring that issue and found poor functional outcome and increased mortality rates among patients who developed sICH after receiving IV rtPA[32]. This might be due to small sample size in our study.

This study showed significant correlation between door-to-needle time and functional outcome at 3 months after receiving IV rtPA. Similar association is also found in other studies[33, 34].

Conclusion

Intravenous thrombolytic therapy improves the overall functional outcome among hyperacute ischemic stroke patients. In patients aged less than 70 years, stroke severity, NIHSS score on admission, door-to-needle time, and onset to needle time could be used as independent predictors of the functional outcome.

Limitations of the Study

Our study was performed in a single center; therefore, the sample size was small. It included only those who completed the follow-up at 3 months after receiving IV rtPA. However, that follow-up period (3 months) is relatively short to some extent. Also, the study included the major potential variables affecting the functional outcome but there are other variables could affect the outcomes like biomarkers, genetics, history of previous stroke, and infarction volume.

Recommendation

Further prospective cohort studies with larger sample sizes and longer follow-up periods are recommended.

Table 1: Demographic and baseline characteristics

Demographic and baseline characteristics of the patients	No (%)
Gender	
Male	77 (77.0)
Female	23(23.0)
Age	
Min.–Max.	30-80
Mean ± SD	53.97±12.89
Median	55 (50-59)
Risk factors	
DM	18 (18.0)
HTN	60 (60.0)
IHD	1 (1.0)
AF	1 (1.0)
door-to-needle time	
<60 min	85 (85.0)
≥60 min	15 (15.0)
Onset to needle time	
<3 hours	39 (39.0)
3-4.5 hours	61 (61.0)

Table 2: Clinical and radiological characteristics of the patients

Clinical characteristics of the patients	No (%)
Symptoms	
Hemiparesis	98 (98.0)
Speech difficulty	67 (67.0)
Facial deviation	66 (66.0)
NIHSS score	
On admission	
Min.–Max.	2-22
Mean ± SD	9.45 ±4.56
At 24-hours rtPA	0-24
Min.–Max.	5.71 ±5.92
Mean ± SD	
Stroke severity (based on NIHSS score)	16 (16.0)
Mild (<5)	39 (39.0)
Moderate (5-9)	45 (45.0)
Severe (>9)	
Stroke location	
Anterior circulation	100 (100)
Posterior circulation	0.0
ASPECTS score	
Min.–Max.	7-10
Mean ± SD	9.38 ±1.12
Hemorrhage post rtPA	
Asymptomatic intracerebral hemorrhage	5 (5.0)
Symptomatic intracerebral hemorrhage	3 (3.0)
No hemorrhage	92 (92.0)

Table 3: Functional outcome and mRS score at 3 months after IV rtPA

Functional outcome of IV rtPA	No (%)
Good functional outcome (0–2)	70 (70.0)
Poor functional outcome (3–6)	30 (30.0)
mRS score 3 months after IV rtPA	
0	37 (37.0)
1	21 (21.0)
2	12 (12.0)
3	6 (6.0)
4	6 (6.0)
5	1 (1.0)
6	17 (17.0)
Min.–Max.	0-6
Mean ± SD	1.94±2.2

Table-4: Association of study variables with functional outcome

Factor	Odds Ratio; 95% CI	p value
Age < 70 years	0. 31; 0.15-0.71	0.008
Gender	1.02; 0.37-2.83	0.57
DM HTN	0.46; 0.15-1.6 0.67; 0.27-1.5	0.16 0.12
NIHSS Score <10	0.06; 0. 04-0.52	0.001
door-to-needle time < 60 min	0.4; 0.09-0.94	0.02
door-to-needle time > 60 min	3.27; 1.06-10.1	0.02
Onset to needle time < 3 hours	0.93; 0.75-1.24	0.14
Onset to needle time 3-4.5 hours	1.58; 1.15- 2.78	0.03

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