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Safety and Clinical Effectiveness of Alteplase in Acute Ischemic Stroke: A prospective Observational study.

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Abstract:
Background: Alteplase is used in Acute Ischemic Stroke (AIS) patient reaching hospital within recommended time window. However, it has potential to cause heamorrhage. Data regarding its incidence of heamorrhage and effectiveness in clinical setting in Indian population is limited. This observational study was undertaken to analyse safety and effectiveness of Alteplase in Acute Ischemic Stroke Patients in Indian clinical setting .
Materials and Methods: AIS Patients who were administered Alteplase in this hospital from February 2017 to June 2018 were enrolled. NIHSS (National Institute of Health Stroke Scale) score was assessed before thrombolysis, 2 hour after thrombolysis and 24 hour after thrombolysis. Modified Rankin Score (mRS) was assessed on day 7 or earlier and on day 90.
Results: 22 patients were enrolled with a mean age (60.86±13.01) Year and median NIHSS Score of 11. 72. 73% showed improvement by atleast 1 point on NIHSS at 24 hour. 27.27% had improvement by ≥4 points on NIHSS. 68.42% of patients had mRS score ≤ 2 on day 90. Mortality rate was 13.63%. Total 5 patients (22.73%) developed bleeding.
Conclusion: Alteplase is an effective thrombolytic agent. Bleeding is a major problem associated with Alteplase but it is not always clinically significant. Even though mortality is high but maximum patients shows favourable outcome on long term follow up.
Key Word: Ischermic stroke, rt-PA, safety and efficacy, alteplase,thrombolysis.

I. Introduction

Stroke is a major public health problem worldwide. The Global Burden of Disease study (GBD) 2013, has reported that there were about 6.5 million deaths due to stroke worldwide and stroke was the second most common cause of death after ischemic heart disease and third most common cause of disability.[1]In developing countries like India, cerebrovascular disease is one of the leading causes of death, disability and poses a significant economic burden. The disability – adjusted life - year (DALY) loss in India due to stroke is 10 per 1000 population whereas in USA it is only 4 per 1000 population. Prevalence of stroke in urban Indian population is estimated to be 334-424/100000 while it is about 84-262/100,000 in rural population.[2]The estimated incidence rate of stroke in various parts of India ranges from 119 to 145/100000 population.

The National Institute of Neurological Disorder and Stroke (NINDS) first demonstrated clinically significant benefits with the use of tissue plasminogen activators (rt-PA) in ischemic stroke patients in 1995[3]. Thrombolytic therapy using rt-PA has now been recommended for medical treatment of acute ischemic stroke patients attending the hospital within 4.5 hour of its onset. However, it is associated with a significant risk of intracranial haemorrhage and other major and minor bleeding episodes. Though it is being used in 1-6% of stroke patients in developed countries its use is limited in developing countries like India. The underlying reasons for its limited usage of thrombolytic therapy in developing countries are delay in transporting the patients to the tertiary care center, high cost of thrombolytics and lack of proper facilities for timely administration and monitoring of its usage. However, in recent times usage of intravenous thrombolytics in India is rapidly increasing. A study by *Pandian JD et al* showed that the number of patients treated with intravenous rt-PA in 2011 was approximately double as compared with 2009[2]. The Indo-US collaborative National stroke registry in 2013 reported thrombolysis in 11% of stroke patients.

Bangur Institute of Neurosciences (BIN) in Kolkata is the premier tertiary care, teaching hospital with facilities to carry out thrombolysis in acute ischemic stroke.

Although rt-PA is being used in India for acute ischemic stroke, there is limited data from our country regarding its clinical effectiveness in terms of neurological improvement and functional improvement along

with its safety profile. Hence this proposed observational study was undertaken in an attempt to find the safety profile and clinical effectiveness of alteplase in acute ischemic stroke.

II. Material And Methods

This prospective observational study was conducted in joint collaboration by Department of Pharmacology, IPGME&R and Department of Neuromedicine , Bangur Institute of Neurology from February 2017 to November 2018. Subject enrolment was done in department of neuromedicine. Total 22 numbers of adult patient aged ≥18 years (both female and male) with a clinical diagnosis of acute ischemic stroke was enrolled .

Study Design: Prospective Observational Study.

Study Location: This was a tertiary care teaching hospital based study done in joint collaboration by Department of Pharmacology, IPGME&R and Department of Neuromedicine , Bangur Institute of Neurology, Kolkata West Bengal.

Study Duration: February 2017 to November 2018.

Sample size: 22 patients.

Sample size calculation: Since the study was planned as a time bound observational study, no formal sample size calculation was undertaken. Review of past thrombolysis in the hospital records indicated that we could enroll about 25-30 thrombolytic patients within our study period. In this study we were able to recruit only 22 subjects within the study period since thrombolysis of acute ischemic stroke was temporarily stopped for about 4 months during the study period due to some technical and logistics issues.

Subjects & selection method: All acute ischemic stroke patients, admitted in the neuromedicine ward of Bangur Institute of Neuroscience from February 2017 to June 2018 and had been administered Alteplase were enrolled.

Inclusion criteria:

1. Adult patients (age >18 years) of either gender with a clinical diagnosis of Acute Ischemic Stroke admitted in the Neuromedicine department of BIN and given thrombolytic treatment with intravenous alteplase
2. Patient or patient's caregiver willing to provide written informed consent.

Exclusion criteria:

1. History of head injury within last 3 months.
2. Major surgery in preceding 14 days.
3. GIT bleeding in preceding 21 days.
4. Recent myocardial infarction.
5. Sustained BP >185/110 mm of Hg despite treatment.
6. Plasma glucose <50mg/dl or >400mg/dl.
7. Use of heparin within last 48 hours

Procedure methodology

The study commenced after approval of the study protocol by the IPGMER Institutional Research Ethics Committee. Written informed consent was taken from all study subjects prior to enrolment in the respective vernacular (Bangla or Hindi or English) version of the informed consent form. A study specific case record form (CRF) was designed for data collection. Demographic profile of the patient, date and time of stroke and time of alteplase administration were noted. Detailed medical history like past history of any cerebrovascular or cardiovascular events, history of hypertension, diabetes mellitus and past use of any anti-platelet drugs were recorded. Laboratory parameters such as hemoglobin, random blood sugar level, urine RE/ME and occult blood test report were recorded. National Institute of Health Stroke Scale (NIHSS) score was assessed before thrombolysis, at 2 hour and at 24 hour after the administration of alteplase by the attending clinician. Imaging studies CT/MRI report of brain are done routinely for all stroke patients who are thrombolysed before and 24-36 hour after thrombolysis. The reports of these investigations were recorded. Regular follow up of each recruited patient during hospital stay was done till outcome i.e discharge/ death/ discharge against medical advice. Assessment of short term functional outcome was done by the Modified Rankin Scale (mRS) at day 7 or earlier (if discharged earlier) and the long term functional outcome assessment on day 90 at the follow up visit. As the study was mainly an in-hospital setting so each enrolled patient was regularly followed up by reviewing all hospital clinical and treatment records during the entire hospital stay till outcome i.e death/discharge/discharge against medical advice. Following discharge the subjects routinely attend the stroke OPD and the long term functional outcome assessment was done at day 90 (i.e 3months) from the day of thrombolysis. A window period of seven days was allowed for the last assessment visit.

Statistical analysis

Study data which was collected in the case record form and then transcribed onto the MS Excel spreadsheet and analysed using SPSS (Statistical Package for Social Sciences, version 16.0.1 of IBM, USA) and GraphPad Prism version 5.0 of GraphPad software, USA. All study variables were summarized using appropriate measures of central tendency and dispersion. For numeric data with normal distribution, mean and standard deviation (SD) was computed and for numeric non parametric data median and interquartile range (IQR) was calculated. For categorical variables, frequency (counts) and percentage was computed. For comparing the scores (NIHSS and MRS) at different study visits the Friedman ANOVA test or repeated measure ANOVA tests was used based on the distribution pattern of the study data. For comparing categorical data Fisher's test or Pearson's Chi square test was done and for comparing numeric data Wilcoxon paired test was done.

III. Result

The baseline characteristics and disease profile of the study population are presented in Table 1a. A total of 22 patients who underwent thrombolysis in BIN spanning over a period from February 2017 to June 2018 were enrolled in the study. All thrombolised patients were confirmed cases of acute ischemic stroke by clinical examination and confirmed by imaging (CT scan/ MRI brain). As per eligibility criteria no patient had history of head injury within past 3 months, major surgery in preceding 14 days or GIT bleeding in preceding 21 days.

The mean (SD) age of patients when thrombolysis was undertaken was 60.86 ± (13.01) years. Age of patients who underwent thrombolysis ranged from 38 to 86 years with minimum age of 38 years and maximum age of 86 years. The median age of enrolled patients was 59 year. Age stratification revealed that 11 patients (50%) were in the 41 – 60 year age range; 7 patients (32%) in 61 to 80 years range. There were only 2 patients above 80 year of age. Gender stratification revealed that 17 patients (77.27%) were male and 5 patients (22.72 %) were female. Patients were urban residents of Kolkata and its adjacent districts. Review of other important medical disorders revealed that 15 patients (68.2%) were hypertensive, 6 patients (27.3%) were diabetic, 4 patients (18.2%) had past history of stroke and 1 patient (4.5%) had past history of ischemic heart disease. Only 2 patients (9.1%) gave history of antiplatelet drug intake. Majority of the hypertensive patients were not on regular antihypertensive drug therapy and they did have documented records of adequate BP control. Table 1b depicts the time interval between onset of stroke symptoms to administration of alteplase. Figure 1 depicts the frequency distribution of patients thrombolised in different time window. The mean time taken by enrolled patients from onset of symptoms to administration of alteplase was 243.90 ± 61.65 min (4.065±1.02h). The time interval ranged from 120 min to 395 min. Only 2 patients could be thrombolised within 3 hour (180 min) time window. Maximum patients (77%) were thrombolised between 3 to 5 hour time window. There were three patients who were thrombolised beyond 5 hour time window and out of those 3 patients 1 patient was thromblised after 6.5 hour since symptom onset.

Table 1a: Baseline characteristic and disease profile of the study population.

Variable **n=22**	**Frequency (%)**
Age in (yr) • 18 ≤ 40 • 41 ≤ 60 • 61 ≤ 80 • >80	 2 (9%) 11 (50%) 7 (32%) 2 (9%)
Gender • Male • Female	 17 (77.27 %) 5 (22.72%)
History of hypertension	15 (68.2%)
Past history of CVA	4 (18.2%)
Past history of AMI	1 (4.5%)
History of diabetes	6 (27.3%)
History of intake of antiplatelet drugs	2 (9.1%)

CVA- cerebrovascular accident AMI- acute myocardial infarction

Figure 1: Time since stroke onset to thrombolysis

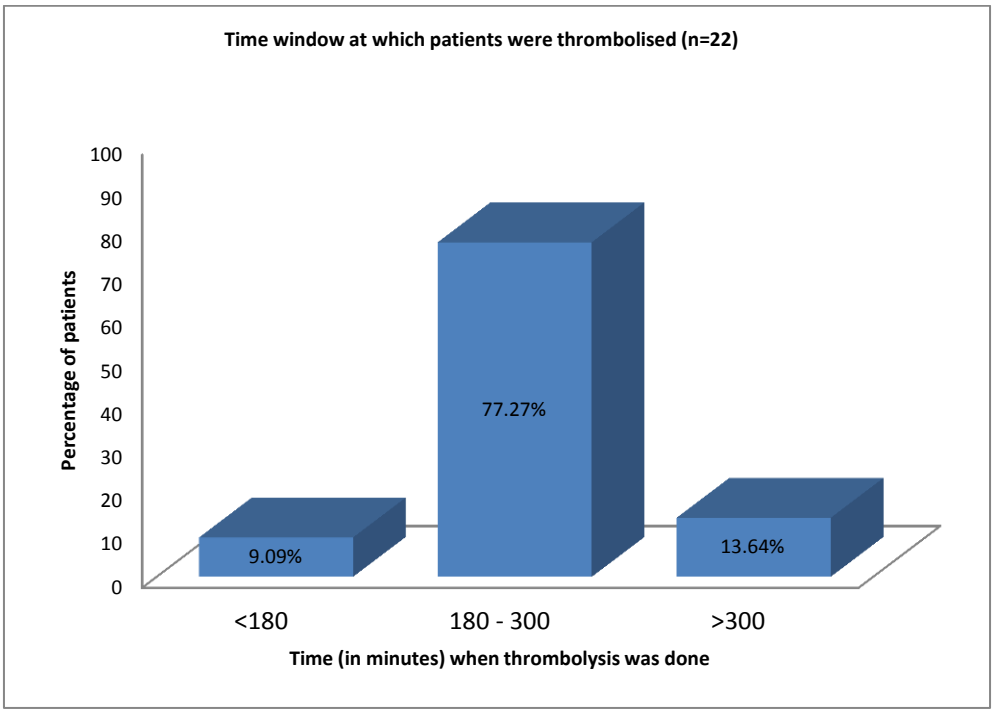


Table 1b: Time interval between onset of stroke symptoms and administration of altepalse

Parameter	**Values**
Time (min) Mean ± SD Range	 243.90 ± 61.65 120 to 395
Categories • < 180 min • 180-300 min • >300 min	 2 (9.09%) 17 (77.27%) 3 (13.64%)

Assessment of neurological improvement in the entire study population :

National Institute of Health Stroke Scale (NIHSS) score was assessed before thrombolysis, 2 hr after thrombolysis and 24 hour after thrombolysis for each enrolled patients. Table 2a and 2b show the NIHSS score at different time points and its comparison. The baseline NIHSS score ranged from 4.0 to 26.0 with median value of 11 and interquartile range of 6 to 13. The NIHSS score after 2 hours ranged from 2.0 to 25.0 with median value of 8.0 and interquartile range of 6 to 10. The NIHSS score after 24 hours following alteplase administration ranged from 0 to 26.0 with median value of 6.5 and interquartile range of 4 to 11. The statistical significant test using Freidman's ANOVA to test significant changes in median value following thrombolysis revealed a highly significant p-value of $p<0.00001$. Table 2b depicts changes in NIHSS score from baseline following alteplase administration. More than or equal to 4 points reduction in NIHSS score from baseline signifies clinically significant improvement. Analysis revealed that only 3 patients (13.63%) and 6 patients (27.27%) had ≥4 points reduction in NIHSS score from baseline at 2 hour and 24 hour respectively. There were 12 patients (54%) who had less than 4 points reduction in NIHSS score at 2 hour. There were 11 patients (50%) who had less than 4 points reduction in NIHSS score at 24 hours. Further analysis revealed that 7 patients (31.31%) at 2 hour and 5 patients (22.72%) at 24 hour had either no changes in NIHSS score or increase in NIHSS score. Increase in NIHSS score means clinical deterioration.

Table 2a: Comparison of NIHSS score at different time points following thrombolysis with alteplase

Variable n=22	**Range**	**Mean ± SD**	**Median**	**Interquartile range**
NIHSS before thrombolysis	4.0 to 26.0	10.64 ± 5.019	11.0	6 to 13
NIHSS 2hr after thrombolysis	2.0 to 25.0	8.91 ± 5.172	8.0	6 to 10
NIHSS 24hr after thrombolysis	0 to 26.0	8.09 ± 6.465	6.5	4 to 11
Friedman's ANOVA	p<0.00001			

NIHSS- National Institute of Health Stroke Scale.

Table 2b: Proportion of cases showing "early neurological improvement" in NIHSS score at different time points

Changes in NIHSS score, n (%) n=22	**At 2 hour**	**At 24 hour**
≥4 point reduction on baseline NIHSS score	3 (13.64%) 95% CI 4.75 to 33.34%	6 (27.27%) 95% CI 13.15 to 48.15%
<4 points reduction on baseline NIHSS score	12 (54.55%) 95% CI 34.66 to 73.08%	11(50%) 95% CI 30.72 to 69.28%
No reduction or increase in NIHSS score from baseline	7 (31.82%) 95% CI 16.36 to 52.68%	5 (22.73%) 95% CI 10.12 to 43.44%

68.18% of subjects (15 out of 22) showed at least one point improvement in the NIHSS score at 2 hours post thrombolysis whereas the rest showed either no improvement or worsening.
72.73% (16 out of 22) showed improvement by at least 1 point at 24 hrs while the rest did not.

Assessment of neurological improvement in subgroups :
Subgroup analysis was done for cases who underwent thrombolysis within 300 mins (n=19) and those who underwent it after 300 mins (n=3). The data are represented in tables 2c and 2d respectively.

Table 2c: Subgroup analysis of patients who underwent thrombolysis within 300 min

Parameters (n=19)	**Value**
Baseline NIHSS Score Mean ± SD Median (IQR)	 9.73± 3.73 11
NIHSS score after 24 hour Mean ± SD Median (IQR)	 7.31±5.47 6
No. patients with mRS score ≤ 2 on day 7	8 (42.11%) 95% CI 23.15 to 63.73
No. of patients with 2mRS score ≤ on day 90	13 (68.42%) 95% CI 56.01 to 84.63%
Mortality	2 (10.53%) 95% CI 2.94 to 31.4%
Length of hospitalization (days) Mean ± SD Median	 8.57±6.79 7

No. of patients who had bleeds at neurologic and/or non neurologic sites n (%)	5 (26.32%) 95% CI 11.81 to 48.8%

There were 3 patients who were thrombolysed after 5 hrs and a subgroup analysis of these cases has been shown in table 2d. Their baseline mean NIHSS score was 13.36±6.80 and the NIHSS score after 24 was 10.5±7.86. There were no patients who had ≤2 mRS score on first follow- up and there was only 1 patient with ≤ 2 mRS score on day 90. Mean length of hospitalisation was 7.66 days, haemorrhage occurred in 1 patient which resulted in death. Since the number of cases were less than 6 we could not compare functional outcomes between groups.

Table 2d: subgroup analysis of patients who were thrombolised after 5 hour (300 min)

Parameters (n=3)	**Value**
NIHSS Score before thrombolysis Mean ± SD Median (IQR)	 16.33±9.07 15 (9.75 to 23.25)
NIHSS score after 2 hour Mean ± SD Median (IQR)	 15± 8.88 12 (9 to 21.75)
NIHSS score after 24 hour Mean ± SD Median (IQR)	 13 ±11.26 7 (6.25 to 21.25)
No . patients with mRS score ≤ 2 on day 7	0
No. of patients with 2mRS score ≤ 2 on day 90	1
Mortality	1 (33.33%) 95%CI 6.15 to79.23%
Length of hospitalization (days) Mean ± SD Median (IQR)	 3.66 ±2.30 5 (2 to5)
No. of patients who had bleeds at neurologic and/or non neurologic sites n (%)	0

Assessment of functional outcome in the entire study population:

Modifies Rankin Score (mRS) was assessed at day 7 or earlier and on 90th day following thrombolysis to assess the number of thrombolised patients with functional independence. Figure 2 shows the number of patients with mRS score of thrombolised patients at different time point. Analysis of mRS score on day 7 or earlier revealed that there were 8 (36.36%, 95% CI of 19.73 to 57.04%) patients with ≤2 mRS score which indicates favourable outcome. On day 90, the mRS score was evaluable only on 19 subjects as 3 had died before assessment. Analysis revealed that there was a favourable outcome in 13 (68.42%) 95% CI of 46.01 to 84.63% patients with ≤ 2 mRS score.

Figure 2: Changes in mRS score and mortality at different time point

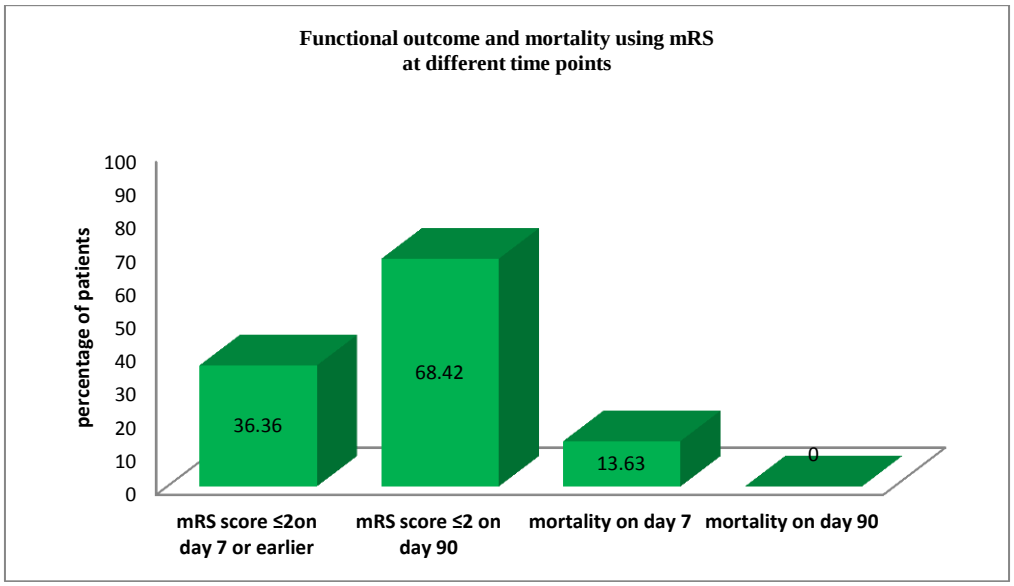


Table 3 shows the comparison of mRS score of thrombolised patients at different time point and comparison of mean mRS score at day 7 or earlier and day 90 revealed a statistically significant change (p=0.0081) using Wilcoxon test (paired sample comparison)

Table 3: Comparison of mRS scores at different time points

Variable n=19	**Range**	**Mean (SD)**	**Median (IQR)**
mRS at day 7 or earlier	0 to 5	3.36 ±1.73	3 (2 to 4)
mRS at day 90	0 to 5	2.21±1.71	2 (1 to 3.75)

mRS-Modified Rankin Score

Safety assessment of thrombolised patients:

To assess the safety outcome following theombolysis, all bleeding episodes were recorded. Table 4 shows the various types of bleeds, frequency of bleed following administration of alteplase. Analysis of bleeding episode revealed that there were a total of 6 adverse events of bleeding at neurologic or non neurologic site. In the underlying table the site of bleeding events are depicted and there were a total of 5 (22.73%) 95% CI 10.12 to 43.44% patients who had developed bleeding from at least one site. Only 1 patient had multiple site bleeds (GI bleed and haematuria) while the others had only one site bleed.

Table 4: Analysis of neurologic or non neurologic site bleeding events

Type of bleed n=22	**Frequencies (%)**
Mucocutaneous	1 (4.55%) 95% CI 0.81 to 21.8%
Gastrointestinal	2 (9.09%) 95% CI 2.53 to 27.81%
Haematuria	1 (4.55%) 95% CI 0.81 to 21.8%
Intracerebral	2 (9.09%) 95% CI 2.53 to 27.81%
Total	6 events

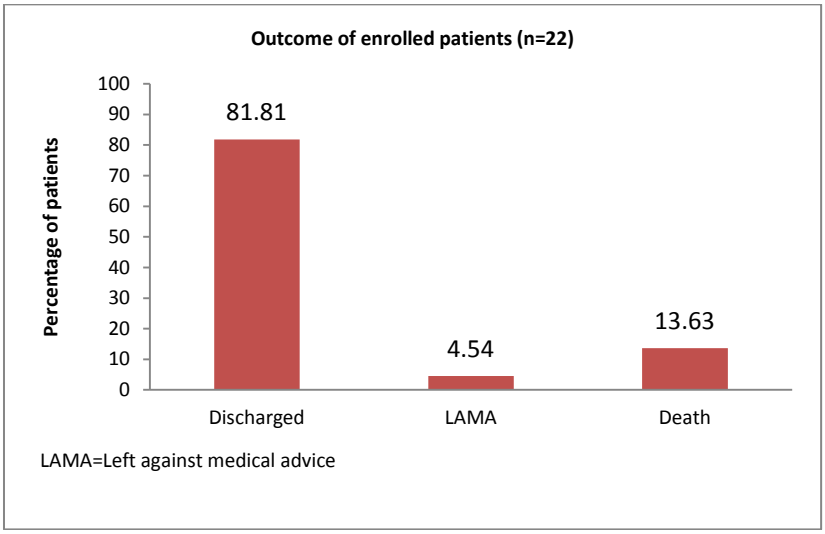
Table 5 and Figure 3 show the in-hospital outcome of enrolled patients following thrombolysis.

Analysis revealed that out of 22 cases 3 patients (13.63%) died in the hospital, 18 patients (81.81%) were discharged from the hospital and 1 patient (4.54%) left against the medical advice. All the bleeding events occurred in patients who were thrombolysed within 300 mins. Of the 2 patients who had intracerebral bleed one succumbed and the one who had mucocutaneous bleed also died.

Table 5: Outcome analysis

Variable N=22	**Frequency (%)**
Discharged	18 (81.81%)
Left against medical advice	1(4.54%)
Death	3 (13.64%)
Duration of hospital stay in days Mean ± SD Median (IQR)	 7.90 ± 6.56 6 (5 to 9)

Figure 3: **Outcome of patients enrolled in the study**



IV. Discussion

Cerebrovascular disease or stroke is one of the leading cause of death and disability worldwide. It is a major public health problem in the world as well as in India. In fact, it is the second most common cause of death after ischemic heart disease and third most common of cause of disability globally. Thrombolysis is the standard treatment modality for ischemic stroke. Although alteplase is being used in the developed countries widely for ischemic stroke, its usage in India is somewhat limited. In recent times, alteplase use in India is increasing but data regarding its safety and clinical effectiveness in Indian population is limited. Though effective for acute ischemic stroke, alteplase has the potential to cause both minor and major bleeding. Many previous studies from various parts of the world have also reported higher incidence of intracerebral haemorrhage associated with alteplase use but safety data from our country regarding major and minor bleeding incidence is limited. Few studies carried out in our country have reported only the major bleeding incidence associated with the drug and also studies were done with very small sample size. Hence this proposed observational study was undertaken in an attempt to find the safety profile and clinical effectiveness of alteplase in acute ischemic stroke. The data generated from this study will help in the decision making of physician as well as in government health care policy.

This prospective observational study was carried out at a premier neurosciences specialist government teaching hospital of Kolkata. Our study has assessed the safety profile of alteplase administration in acute ischemic stroke by observing the frequencies of major and minor bleeding episodes. The clinical effectiveness of alteplase was assessed by neurological improvement using a standardized stroke rating scale the National

Institute of Health Stroke Scale (NIHSS) at 2 hrs and 24-36hrs following alteplase administration. The functional outcome of patient was also assessed using Modified Ranking Score (mRS) on 7th day or earlier and on 90th day. The study was carried out over a period of 16 months from February 2017 to June 2018.

During the study period 22 patients were enrolled. Most of the patients belonged to the elderly age group and the mean age of the study population was 60.86±13.02 years. The mean age in our study was slightly lower than the mean age found in ECASS 3 study (64.9±12.2)[4].

Gender stratification revealed male preponderance in our study. A similar study done at AIIMS, New Delhi which also showed similar trends (57.40%)[5]. This suggests that the incidence of ischemic stroke is higher among males population.

Analysis of proportion of hypertensive patient revealed that majority of enrolled subject had a history of hypertension similar to previous reported studies. This clearly suggests that hypertension is one of the important causes of ischemic stroke.

Analysis of past medical history revealed that diabetes, myocardial infarction and history of prior stroke was some important risk factor for ischemic stroke.

The mean time taken by patients from onset of stroke symptoms to administration of alteplase in the hospital was 243.90±61.65 minute (4.06±1.027 hour). Our study suggests that in clinical setting only a small proportion of ischemic stroke patients are being thrombolised within 3 hour time window recommended by NINDS study. Many previous studies have demonstrated that earlier initiation of treatment is associated with better outcome in terms of both effectiveness and safety. *Hacke W et al* carried out a pooled analysis of ATLANTIS, ECASS and NINDS rt-PA stroke trials and showed that treatment with alteplase was nearly twice as efficacious when administered within the first 1.5 hours after the onset of stroke as it was when administered within 1.5 to 3 hours afterwards[6].

The median baseline NIHSS score in our study population was 11 and after 2 h following alteplase administration median values came down to 8 and 6.5 after 24 hr. The changes in NIHSS score from the baseline score at different time point following alteplase administration was highly significant ($p<0.0001$) which is a clear indication of alteplase activity in opening up the occluded vessels. In NINDS trial the mean baseline NIHSS score was 14. Similar baseline mean values were also observed in study by *Palanisamy S et al* and *Padma MV et al.*

Compared to other studies, our study showed very less proportion of patients improving significantly after 24 h following alteplase administration. But the proportion of patients having significant improvement increased to twice at 24 h as compared with proportion at 2 h , implying that time factor also plays a role in the NIHSS score outcome. Majority of the patients showed some neurologic improvement following alteplase administration even though the extent of improvement was not major.

The mean NIHSS score after 24 h in those who were thrombolised within 300 min was 7.31 ± 5.47 whereas those who were thrombolised after 300 min had mean NIHSS score of 13 ± 11.26 after 24 h post thrombolysis . The significant difference in mean NIHSS score suggests that early initiation of treatment is crucial for better outcome.

There was clear difference in the proportion of patients with favourable outcome (mRS score ≤2) in those who were thrombolised within 300 min (42.11%) and those who were thrombolised after 300 min (0%). This observation further clarifies the importance of early initiation of treatment.

Functional outcome of the patients was measured using modified rankin scale (mRS). This measure signifies the sustained clinical benefit of the drug. Those patients who had 0 to 2 mRS score were considered as favourable outcome because mRS score ≤ 2 means the patient is functionally independent and doesn't require assistance in carrying out daily activities. Accordingly, we analyzed the number of patients having ≤2 mRS score on day 7 or before discharge from the hospital and on day 90. The analysis revealed that there were 8 patients (36.36%, n=22) who had favourable outcome on day 7). On day 90, the mRS score was evaluable only on 19 subjects as 3 had died before assessment and a favourable outcome was observed in 13 (68.42%) patients..

In order to assess the safety outcome following alteplase administration, we recorded all major and minor systemic bleeding episodes as well as symptomatic and asymptomatic intracerebral haemorrhage. Any systemic bleeding which was life threatening and resulted in a decrease in the haemoglobin of ≥5mg/dl or that required more than 2 units of blood cell transfusion was considered a major systemic haemorrhage. Analysis of bleeding episodes revealed that there were a total of 6 adverse events of bleeding at neurologic or non neurologic site. There were 5 patients (22.73%) who developed bleeding from at least one site. Only one patient had multiple site bleeding (GI bleeding and haematuria). All systemic bleedings were minor bleedings as per definition and only 2 patients developed intracerebral haemorrahage out of which one was a symptomatic

intracerebral haemorrhage (sICH) and the patient later died. Another patient who developed asymptomatic ICH had very high baseline NIHSS score (17).

Review of safety outcome of previous studies revealed that in NINDS studies rate of symptomatic intracerebral haemorrhage was 6.4% whereas in our study it was 4.54% while in the ECASS 3 study it was 2.4%. Study by *Padma MV et al* in AIIMS new Delhi showed that intracerebral haemorrhage occurred in 9% of the study population but none had sICH. The study by *Palanisamy Sivanandy et al* in south India, which was very much similar to our study protocol showed 8.7% sICH which was slightly higher than our findings.

We also analyzed the in-hospital outcome of the patients enrolled in our study. Analysis revealed that maximum patients (18; 81.81%) were discharged from the hospital. The in-hospital mortality was 13.64% whereas in the SITS-MOSTS study it was 10%[7]. The median length of hospitalisation was 6 days in our study whereas in the SITS-MOSTS study it was 7 days. In the *Padma MV et al* study the mean length of hospitalisation was 9 ± 9 days whereas in our study the mean length of hospitalisation was 7.90 ± 6.56 days.

Strength of our study: To the best of our knowledge perhaps this is the first study undertaken in a government hospital from eastern India evaluating the safety and clinical effectiveness of alteplase in acute ischemic stroke. In addition to symptomatic and asymptomatic intracerebral haemorrhage, and other non neurologic major systemic bleeding we also evaluated the minor systemic bleeding. In order to detect minor internal systemic bleeding like gastrointestinal and urinary tract bleeding which are usually undetectable by general examination, we evaluated occult blood test and microscopic urine examination in each patient post thrombolysis. Such a thorough evaluation was possibly not reported in other similar Indian studies. Our study will be of great help to clinician as well as the administrative authorities in decision making. Many of the treating physicians are still not sure about the efficacy of this drug and also they are always in fear due to potential of this drug to cause fatal haemorrhage. Our study will provide them greater insight of the drug safety and efficacy.

Limitation of our study: This prospective observational study had some limitations that are inherent of observational study design. Sample size was dependent on the number of thrombolysis cases taking place in our hospital setting. Therefore, a large cohort could not be enrolled within the stipulated time period. Assessment of mRS score at 1 month could have provided greater insights of the sustained benefit of the drug. Due to small sample size the outcome may not be generalizable.

Finally, this being an observational study the advice for undertaking laboratory and other imaging investigation are more pragmatic and more dependent on the standard hospital practice guidelines and not driven for research outcome assessment.

V. Conclusion

Alteplase is an effective thrombolytic agent. Bleeding is a major problem associated with alteplase but it is not always clinically significant. Even though mortality rate is high but maximum patients shows favourable outcome on long term follow-up. Further study with larger sample size and longer follow up may provide further insights about the long term functional outcome following thrombolysis with alteplase.

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