Section: Neurology

Original Research Article

A STUDY OF OUTCOME OF STANDARD VERSUS LOW DOSE THROMBOLYSIS IN ACUTE ISCHEMIC STROKE

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ABSTRACT

Background: The National Institute of Neurological Disorders and Stroke (NINDS) trial published in 1995 was a landmark trial demonstrated improvement in neurologic outcomes at 90 days with a NNT of a favorable outcome to be 7. This led to FDA approval of alteplase in 1996 for thrombolysis in acute ischemic stroke. A larger international study **(ENCHANTED)** which recruited patients from 13 countries including populations from Europe, Asia, South America, and Australia demonstrated that low dose rtPA is not inferior to standard dose of alteplase. Here, we aim to describe the functional outcome at 3 months, post thrombolysis with Standard-dose and Low-dose alteplase and the complications of symptomatic intracranial hemorrhage and death in both.

Materials and Methods: The present study was a cross-sectional hospital based study designated with the aim to study the outcome of thrombolysis with low dose compared to standard dose. A total of 60 acute ischemic stroke patients reporting within 4.5 hours of onset of symptoms were enrolled from, September, 2019 to June, 2021. Patients fulfilling AHA/ASA guidelines (2019 update) for thrombolysis were randomly assigned to receive low dose or standard dose alteplase with a maximal dose limit of 90mg.

Results and conclusions: Thrombolysis with alteplase (rtPA) is very effective in treatment of acute ischemic stroke upto 4.5 hours of onset of symptoms. Lower dose of alteplase was found to be non-inferior to standard-dose of alteplase in terms of efficacy for thrombolysis. Symptomatic ICH is more common in thrombolysis with standard-dose of alteplase as compared to low-dose.

Keywords: Acute Ischemic Stroke, Low-Dose Thrombolysis, Standard-Dose Thrombolysis, Alteplase (rt-PA), Intravenous Thrombolysis, Functional Outcome, Stroke Management.

INTRODUCTION

Stroke is classically characterized as a neurological deficit attributed to an acute focal injury of the central nervous system (CNS) by a vascular cause, including cerebral infarction, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH), and is a major cause of disability and death worldwide.[1]

Stroke is defined by World Health Organization as "a clinical syndrome of rapidly developing clinical signs of focal disturbance of cerebral function, lasting more than 24 hours, or leading to death, with no apparent cause, other than that of vascular origin".[1]

The American Heart Association/American Stroke Association published an updated definition of stroke in 2013**. Ischemic stroke** is defined as an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction. **Hemorrhagic stroke** is defined as rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma.[1]

Globally, Stroke is the second-leading cause of death and the third-leading cause of death and disability combined according to latest Global Burden of

Disease study in 2019.[2] Stroke is a significant global health problem and a major cause of mortality and morbidity in developed countries and increasingly in low-middle income countries (LMICs).[3] Seventy percent of strokes occur in LMICs, and the subsequent disease burden is greater than that of high-income countries.[4] Life expectancy in India has recently increased to over 60 years of age,[5,6] leading to an increase in age-related, non-communicable diseases including stroke,[7,8] making stroke India's fourth leading cause of death and fifth leading cause of disability.[9] In a recent systematic review, consisting mainly of cross-sectional studies, the incidence of stroke in India was estimated to be between 105 and 152/100,000 people per year .[10]

During the past three decades, acute stroke reperfusion strategies have evolved from nilhism to thrombolytic therapy followed by endovascular therapy and recently to next generation endovascular devices and thrombolytic agents.[13]

The National Institute of Neurological Disorders and Stroke (NINDS) trial published in 1995 was a landmark trial demonstrated improvement in neurologic outcomes at 90 days with a NNT of a favorable outcome to be 7. This led to the FDA approval of alteplase in 1996 for thrombolysis in acute ischemic stroke.[14]

The main concept of stroke thrombolysis is **"time is brain"** and the thrombolytic agent has to be administered as early as possible. The efficacy of the thrombolytic agent depends on the age of clot, size, and location since the higher density of cross-linking of fibrin makes clot harder, more compact and difficult to dissolve.[15]

Several trials such as the National Institute of Neurological Disorders and Stroke **(NINDS)** and the Europeon Collaborative Acute Stroke Study (ECASS) had proven the benefit of rtPA in acute ischemic stroke within 3 hours.[16,17] Several prospective observational registries like Canadian alteplase stroke effectiveness study registry,[18] and safe implementation of thrombolysis in stroke-international stroke thrombolysis register showed similar rates of mortality, symptomatic intracranial hemorrhage (ICH) within 24 hour and functional independence.[19] An individual patient data (IPD) meta-analysis of the randomized controlled trials (RCTs) showed that thrombolysis using alteplase within 3 hour of stroke onset led to a good outcome.

The ECASS III trial showed the benefit of thrombolysis with alteplase in patients with clearly defined symptoms onset between 3 and 4.5 hours of stroke onset. In the IPD meta-analysis, thrombolysis with alteplase showed benefit for patients with stroke onset within 3 to 4.5 hours.[20] After the result of ECASS III trial, thrombolysis with alteplase is approved from 3 to 4.5 hours in Europe, Australia and many countries including all the leading guidelines. However, US FDA has approved alteplase for thrombolysis only up to 3 hours.

Taiwan Thrombolytic Therapy for Acute Ischemic Stroke (TTT-AIS) study, one of the first study showed that complications were higher (SICH, deaths and dependence at 3 months) in elderly patients receiving a dose of 0.9mg/kg alteplase.[21]

A second larger study in China which tested a range of doses from 0.6 – 0.9 mg/kg suggested that lower doses were associated with better outcomes in older patients.[22]

These observations led to Japan approving a lower than standard dose of rtPA for thrombolysis based on trial data.[23]

Finally, a larger international study **(ENCHANTED)** which recruited patients from 13 countries including populations from Europe, Asia, South America, and Australia demonstrated that low dose rtPA is not inferior to standard dose of 0.9mg/kg of alteplase.[24]

With this study, we aim to describe the functional outcome at 3 months' post thrombolysis with Standard dose (0.9mg/kg) and Low dose (0.6mg/kg) alteplase and the complications of symptomatic intracranial hemorrhage and death in standard as well as in low dose groups.

MATERIALS AND METHODS

The present study was a cross-sectional hospital based study designated with the aim to study the outcome of thrombolysis with low dose compared to standard dose. A total of 60 acute ischemic stroke patients reporting within 4.5 hours of onset of symptoms were enrolled from, September, 2019 to June, 2021. Patients were evaluated, urgent NCCT head was performed, NIHSS and MRS score was calculated. Patients fulfilling AHA/ASA guidelines (2019 update) for thrombolysis were randomly assigned to receive low dose (0.6mg/kg;15% as bolus and 85% as infusion over one hour) or standard dose (0.9mg/kg;10% as bolus and 90% as infusion over one hour) alteplase with a maximal dose limit of 90mg. After thrombolysis, all patients were monitored in Intensive care unit at least for 24 hours and blood pressure was strictly monitored as per AHA/ASA guideline.

RESULTS

The results of the study are as follows: Distribution of TOAST classification was comparable between standard and low dose. (Undetermined etiology: - 11.11% vs 16.67% respectively, Cardio embolic: - 19.44% vs 29.17% respectively, Lacunar: - 25% vs 25% respectively, Large artery: - 38.89% vs 25% respectively, Other: - 5.56% vs 4.17% respectively) (p value=0.778).

No significant difference was seen in NIHSS at pre thrombolysis (p value=0.113), at 24 hours (p value=0.862), on discharge (p value=0.349), at 3 months (p value=0.448) between standard and low dose. Mean ± SD of NIHSS at pre thrombolysis, at 24 hours, on discharge, at 3 months in standard dose was 11.89 ± 4.62, 10.53 ± 7.83, 7.78 ± 5.76, 4.06 ± 4.42 respectively and in low dose was 13.96 ± 5.26,

10.83 ± 5.75, 9.22 ± 5.25, 4.91 ± 3.28 respectively with no significant difference between them.

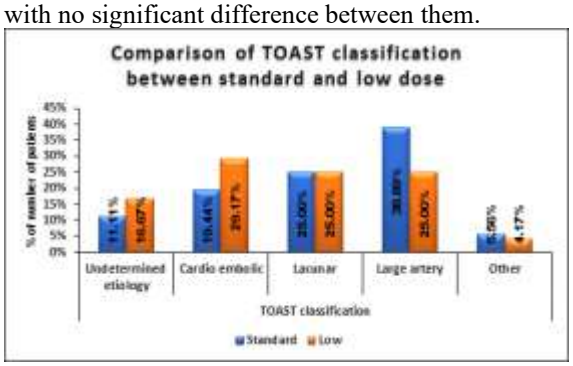

Figure 1: Comparison of TOAST classification between standard and low dose

Figure 4: Comparison of TOAST classification between standard and low dose.

Distribution of TOAST classification was comparable between standard and low dose. (Undetermined etiology: - 11.11% vs 16.67% respectively, Cardio embolic: - 19.44% vs 29.17% respectively, Lacunar: - 25% vs 25% respectively, Large artery: - 38.89% vs 25% respectively, Other: - 5.56% vs 4.17% respectively) (p value=0.778).

It is shown in table 4, figure 4.

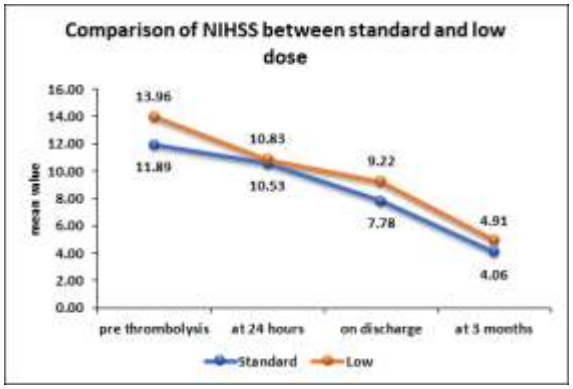

Figure 5: Comparison of NIHSS between standard and low dose

Figure 5: Comparison of trend of NIHSS at different time intervals between standard and low dose.

No significant difference was seen in NIHSS at pre thrombolysis (p value=0.113), at 24 hours (p value=0.862), on discharge (p value=0.349), at 3 months (p value=0.448) between standard and low dose. Mean ± SD of NIHSS at pre thrombolysis, at 24 hours, on discharge, at 3 months in standard dose was 11.89 ± 4.62, 10.53 ± 7.83, 7.78 ± 5.76, 4.06 ± 4.42 respectively and in low dose was 13.96 ± 5.26, 10.83 ± 5.75, 9.22 ± 5.25, 4.91 ± 3.28 respectively with no significant difference between them.

It is shown in table 5, figure 5.

Figure 6: Association of NIHSS with onset to needle time in total study subjects.

No significant association was seen in NIHSS pre thrombolysis (p value=0.272) with onset to needle time in total study subjects. Mean ± SD of NIHSS pre thrombolysis in 0 to 3 hours was 12.14 ± 5.48 and in 3 to 4.5 hours was 13.58 ± 3.99 with no significant association between them.

Significant association was seen in NIHSS at 3 months with onset to needle time in total study subjects. (p value <.05) Mean ± SD of NIHSS at 3 months in 3 to 4.5 hours was 6 ± 3.92 which was significantly higher as compared to 0 to 3 hours (3.47 ± 3.77(p value=0.023)).

Significant decrease was seen in NIHSS at 3 months with respect to pre thrombolysis in both groups: - onset to needle time {0 to 3 hours} (p value<.0001), onset to needle time {3 to 4.5 hours} (p value<.0001).

It is shown in table 6, figure 6.

Table 7: Correlation of age with NIHSS.

Pearson correlation coefficient

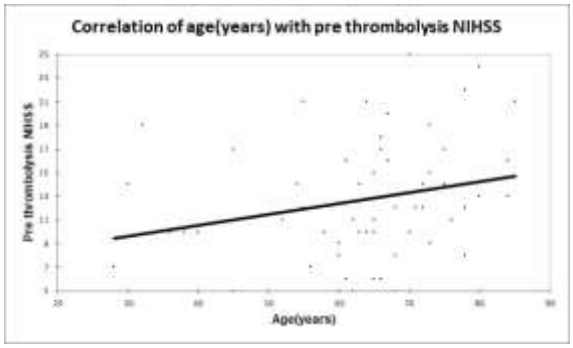

Figure 7.1: Correlation of age(years) with pre thrombolysis NIHSS

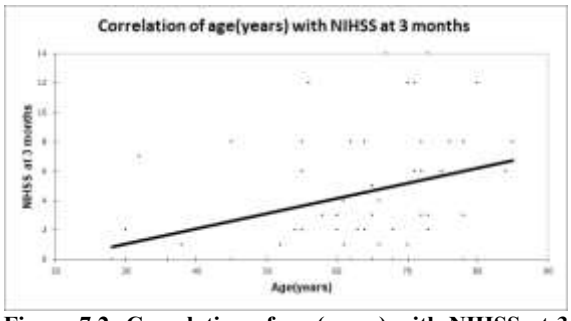

Figure 7.2: Correlation of age(years) with NIHSS at 3 months.

Significant positive correlation was seen between age(years) with NIHSS at 3 months with correlation coefficient of 0.345. Non-significant moderate positive correlation was seen between age(years) with pre thrombolysis NIHSS with correlation coefficient of 0.247.

It is shown in table 7 and figure 7.1, 7.2.

Table 8: Comparison of mRS between standard and low dose

mRS	Standard	Low	Total	P value
Pre thrombolysis				
Mean ± SD	4.19 ± 0.89	4.5 ± 0.51	4.32 ± 0.77	0.097*
Median(25th-75th percentile)	4(4-5)	4.5(4-5)	4(4-5)	

Range	2-5	4-5	2-5	
At 3 months				
Mean ± SD	1.72 ± 1.51	2.14 ± 1.04	1.89 ± 1.34	0.233*
Median(25th-75th percentile)	1(0.75-3)	2(1.25-3)	2(1-3)	
Range	0-5	0-4	0-5	
Intra group p value	<0.0001	<0.0001	-	-

*Independent t test

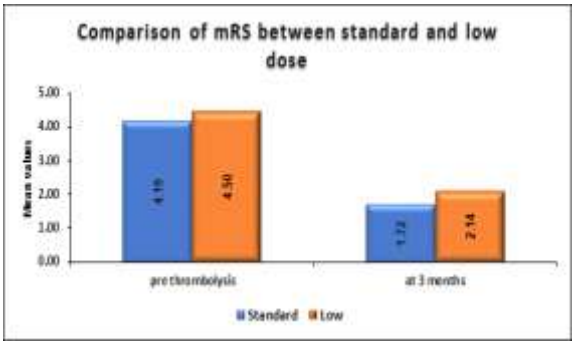

Figure 8: Comparison of mRS between standard and low dose.

No significant difference was seen in mRS at pre thrombolysis (p value=0.097), at 3 months (p value=0.233) between standard and low dose. Mean ± SD of mRS at pre thrombolysis, at 3 months in standard dose was 4.19 ± 0.89, 1.72 ± 1.51 respectively and in low dose was 4.5 ± 0.51, 2.14 ± 1.04 respectively with no significant difference between them

Significant decrease was seen in mRS from pre thrombolysis to 3 months in both groups:-Standard group (p value<.0001) and Low group (p value<.0001).

It is shown in table 8, figure 8..

Table 9: Comparison of mRS at 3 months between standard and low dose

mRS at 3 months	Standard	Low	Total	P value
0	8 (25%)	1 (4.55%)	9 (16.67%)	0.077†
1	10 (31.25%)	5 (22.73%)	15 (27.78%)	
2	3 (9.38%)	8 (36.36%)	11 (20.37%)	
3	6 (18.75%)	6 (27.27%)	12 (22.22%)	
4	4 (12.50%)	2 (9.09%)	6 (11.11%)	
5	1 (3.13%)	0 (0%)	1 (1.85%)	

†Fisher's exact test

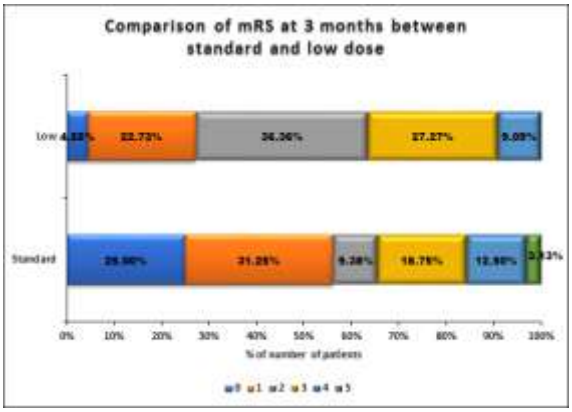

Figure 9: Comparison of mRS at 3 months between standard and low dose

Distribution of mRS at 3 months was comparable between standard and low dose. (0: - 25% vs 4.55% respectively, 1:- 31.25% vs 22.73% respectively, 2:- 9.38% vs 36.36% respectively, 3:- 18.75% vs 27.27% respectively, 4:- 12.50% vs 9.09% respectively, 5:- 3.13% vs 0% respectively) (p value=0.077).

It is shown in table 9, figure 9.

Table 10: Comparison of onset to needle time(hours) between standard and low dose

Onset to needle time(hours)	Standard(n=36)	Low(n=24)	Total	P value
Mean ± SD	2.86 ± 0.69	2.46 ± 0.96	2.7 ± 0.82	0.067*
Median(25th-75th percentile)	3.02(2.287-3.3)	2.42(1.45-3.025)	2.5(2.15-3.188)	
Range	1.5-4.15	1-4.15	1-4.15	

Independent t test

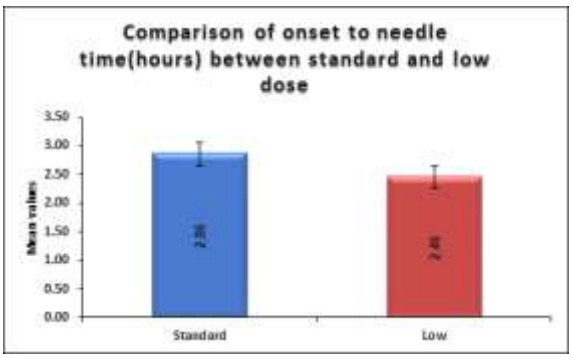

Figure 10: Comparison of onset to needle time(hours) between standard and low dose.

Mean ± SD of onset to needle time(hours) in standard dose was 2.86 ± 0.69 and low dose was 2.46 ± 0.96 with no significant difference between them. (p value=0.067)
It is shown in table 10, figure 10.

Table 12: Vascular Territory of Infarct between standard and low dose

MRI/NCCT brain	Standard(n=36)	Low(n=24)	Total	P value
ACA infarct	1 (2.78%)	1 (4.17%)	2 (3.33%)	0.775†
MCA and ACA infarct	0 (0%)	1 (4.17%)	1 (1.67%)	
MCA and PCA infarct	1 (2.78%)	1 (4.17%)	2 (3.33%)	
MCA infarct	33 (91.67%)	20 (83.33%)	53 (88.33%)	
PCA infarct	1 (2.78%)	1 (4.17%)	2 (3.33%)	
Total	36 (100%)	24 (100%)	60 (100%)	

†Fisher's exact test

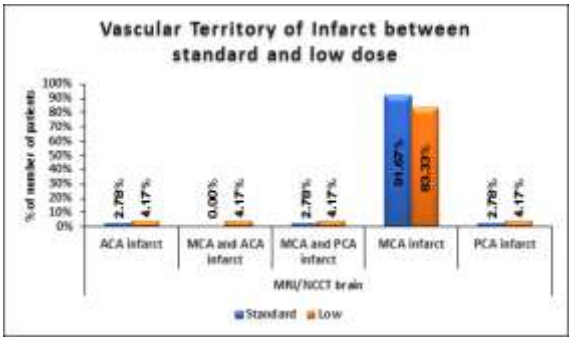

Figure 12: Vascular Territory of Infarct between standard and low dose.

Vascular territory of infarct was comparable between standard and low dose. (ACA infarct: - 2.78% vs 4.17% respectively, MCA and ACA infarct:- 0% vs 4.17% respectively, MCA and PCA infarct:- 2.78% vs 4.17% respectively, MCA infarct:- 91.67% vs 83.33% respectively, PCA infarct:- 2.78% vs 4.17% respectively) (p value=0.775).
It is shown in table 12, figure 12.

Table 15: Comparison of IC bleed between standard and low dose

IC bleed	Standard(n=36)	Low(n=24)	Total	P value
None	18 (50%)	16 (66.67%)	34 (56.67%)	0.202‡
Asymptomatic	9 (25%)	7 (29.17%)	16 (26.67%)	0.721‡
Symptomatic	9 (25%)	1 (4.17%)	10 (16.67%)	0.040†
Total	36 (100%)	24 (100%)	60 (100%)	-

†Fisher's exact test, ‡ Chi square test

Figure 15: Comparison of IC bleed between standard and low dose.

Proportion of symptomatic IC bleed was significantly higher in standard dose (25%) as compared to low dose (4.17%). (p value=0.040)

Distribution of asymptomatic IC bleed and absence of IC bleed was comparable between standard and low dose. (None:- 50% vs 66.67% respectively (p value=0.202), Asymptomatic:- 25% vs 29.17% respectively (p value=0.721).
It is shown in table 15, figure 15.

Table 15.1: Comparison of symptomatic IC bleed between standard and low dose

Symptomatic	Standard(n=36)	Low(n=24)	Total	P value
No	27 (75%)	23 (95.83%)	50 (83.33%)	0.040†
Yes	9 (25%)	1 (4.17%)	10 (16.67%)	
Total	36 (100%)	24 (100%)	60 (100%)	

†Fisher's exact test

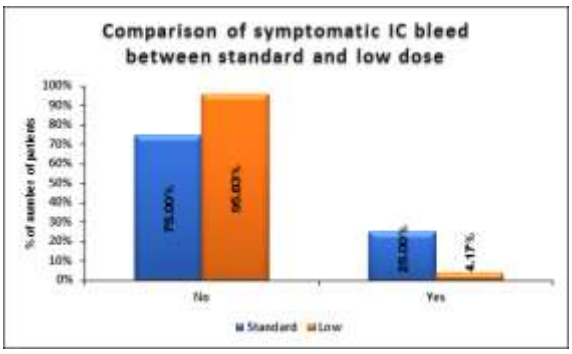

Figure 15.1: Comparison of symptomatic IC bleed between standard and low dose.

Proportion of symptomatic IC bleed was significantly higher in standard dose (25%) as compared to low dose (4.17%). (p value=0.040).

Table 16: Comparison of outcome between standard and low dose

Outcome(mRS at 3 months)	Standard(n=36)	Low(n=24)	Total(n =60)	P value
Independent(0-2)	21 (58.33%)	13 (54.17%)	34 (56.67%)	0.927†
Dependent(3-5)	11 (30.56%)	9 (37.50%)	20 (33.33%)	
Death(6)	4 (11.11%)	2 (8.33%)	6 (10%)	
Total	36 (100%)	24 (100%)	60 (100%)	

†*Fisher's exact test*

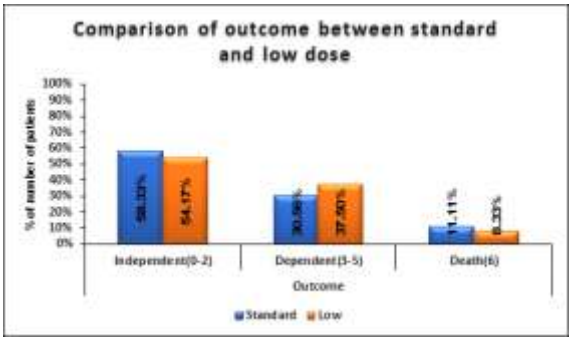

Figure 16: Comparison of outcome between standard and low dose.

Distribution of outcome was comparable between standard and low dose. (Independent(0-2):- 58.33% vs 54.17% respectively, Dependent(3-5):- 30.56% vs 37.50% respectively, Death(6):- 11.11% vs 8.33% respectively) (p value=0.927).
It is shown in table 16, figure 16.

Table 17: Comparison of cause of death between standard and low dose

Cause of death	Standard(n=4)	Low(n=2)	Total	P value
Cardiac arrest	0 (0%)	1 (50%)	1 (16.67%)	0.333†
IC bleed	4 (100%)	1 (50%)	5 (83.33%)	
Total	4 (100%)	2 (100%)	6 (100%)	

†*Fisher's exact test*

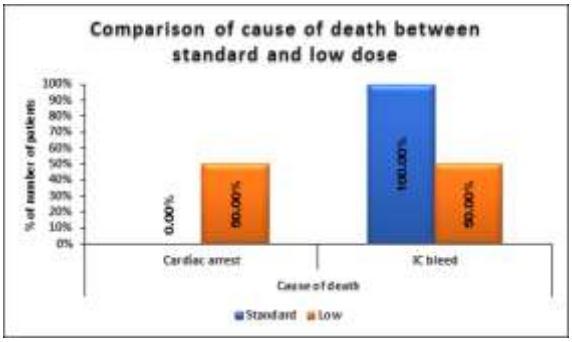

Figure 17: Comparison of cause of death between standard and low dose.

Distribution of cause of death was comparable between standard and low dose. (Cardiac arrest:- 0% vs 50% respectively, IC bleed:- 100% vs 50% respectively) (p value=0.333).

DISCUSSION

The present study was a cross-sectional hospital based study designated with the aim to study the outcome of thrombolysis with low dose compared to standard dose. A total of 60 acute ischemic stroke patients were enrolled from September, 2019 to June 2021, as per the inclusion and exclusion criteria.
Patients were evaluated for severity of stroke by NIHSS score and MRS score, risk factors of stroke and were subjected to NCCT Brain/MRI brain. Eligible patients were thrombolysed with injection alteplase and followed at least for 3 months. Other necessary required investigations were done. Majority of the patients in the study were male. Maximum number of patients were in 6th and 7th decade of life with mean age being 63.33 years (SD=13.3). According to TOAST classification most patients were large artery stroke followed by small

vessel disease, cardioembolic, undetermined etiology and other determined etiology. Mean NIHSS and MRS of study patients were 12.72 (SD=4.95) and 4.19 (SD=0.89) respectively pre thrombolysis. In our study most common co-morbidity was hypertension, followed by dyslipidemia, diabetes mellitus, coronary artery disease, atrial fibrillation and valvular heart disease. MCA territory stroke was most common while the ACA territory infarct was least common. Symptomatic ICH was found in 25% standard dose group while only 4.17% patients had symptomatic ICH in low dose group. Functional outcome of 0-2 (independent) on MRS scale was achieved by 58.33% patients in standard dose group and 54.17% in low dose group. In our study 10% patients died till 3 months of follow up. The most common cause of death was ICH in our study followed by cardiac arrest. None of the patient who died was below 60 years of age.

CONCLUSION

Disclosure
Financial support: None
Conflict of interest: None

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