http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v8i10.02

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

**Original Article**

# Thrombolysis with Alteplase in Acute Ischemic Stroke: A Case Series from A Tertiary Care Centre in Bangladesh

Authors
**Dr Ghulam Kawnayn[1*], Dr Humayun Kabir[2]**
[1]Lt Colonel, FCPS (Medicine), Classified Specialist, CMH, Dhaka, Bangladesh
[2]Colonel, FCPS (Medicine), FCPS (Neurology), Classified Specialist, CMH, Dhaka, Bangladesh
*Corresponding Author
**Dr Ghulam Kawnayn**

**Abstract**
**Background:** *Alteplase is the only licensed thrombolytic agent for the treatment of acute ischemic stroke. The body of evidence to date suggests that it reduces the number of stroke patients who are dead or dependent at follow up, despite the risk of intracranial hemorrhage.*
**Objective:** *The objective of this study was to report our early experience of thrombolysis with alteplase in a case series of acute ischemic stroke.*
**Material and Methods:** *In this case series, profile of patients, onset to hospital time, onset to needle time and door to needle time, and effectiveness and safety of thrombolysis with standard dose (0.9 mg/kg) of alteplase in acute ischemic stroke is reported. Effectiveness of thrombolysis was evaluated by assessing change in National Institutes of Health Stroke score (NIHSS) score. Safety and tolerability of alteplase was evaluated by recording adverse events.*
**Results:** *A total of 10 patients (male n=6, female n=4) with mean age of 63.8 (range 38-84) years were included in this series. Hypertension, diabetes and ischemic heart disease was present in 7(70%), 5(50%) and 2(20%) cases. The mean onset to hospital time, mean onset to needle time and mean door to needle time was 83 (range 0-150) minutes, 187(range 75-240) and 104(range 40-195) minutes. The mean pre-thrombolysisscore was 25.8 which decreased to 8.8 after thrombolysis. Alteplase was well tolerated without any serious adverse event.*
**Conclusion:** *Our initial results with standard dose of alteplase (0.9 mg/kg) as thrombolytic agent are promising. Alteplase was found to be effective in improvement of NIHSS score without risk of serious adverse events.*
**Keywords:** *Alteplase, ischemic stroke, thrombolysis.*

## Introduction

Worldwide, stroke is an important and concerning neurological disorder because of mortality, morbidity and cost associated with it.[1] Globally the burden of stroke is huge. According to recently published data, in 2016, there were 13.7 million new cases of stroke, 5·5 million deaths and 116·4 million DALYs (disability-adjusted life-years) due to stroke. According to the estimates, there were more than 80 million stroke survivors in 2016.[1] The reported prevalence of stroke in Bangladesh is 0.3%.[2] Worldwide stroke

is the second leading cause of death[3] whereas in Bangladesh it is the third leading cause of mortality[2]and important cause of disability.[4]The number of stroke cases is estimated to increase due to increasing number of older people.[5] However, it is important to note that, the condition is also not uncommon in children and adults. According to the data of 2010, there were 5.2 million stroke in subjects less than 20 years of age and adults between 20-64 years of age.[6]A meta-analysis of 53 studies confirmed the importance of recanalization. According to the results of studies, recanalization is strongly associated with improvement in functional outcomes and decreased mortality.[7] A systematic review of published articles reported 17% rate of spontaneous recanalization during the first 6 to 8 hours from stroke onset.[8] Ischemic stroke is more common than haemorrhagic stroke[3] and thrombolytic agents have very important place in its treatment. Safety and efficacy of intravenous recombinant tissue plasminogen activator (r-TPA) is well established in acute ischemic stroke[9,10] Alteplase has been approved for use in acute ischemic stroke.[10,11] Alteplase is one of the common thrombolytics used globally with a standard dose of 0.9 mg/kg.[12] Some studies[12,13,14] have also evaluated efficacy and safety of low dose (0.6 mg/kg) of alteplase. In one study, low dose of aleteplase was not found to be non-inferior to the standard dose with respect to mortality and morbidity at three months. In another study,[13] low dose and standard dose of alteplase were comparable in terms of reduction in major disability. A study suggested that alteplase0.6 mg/kg in Japanese patients may provide clinical efficacy and safety similar to 0.9 mg/kg as seen in patients from North America and European Union.[14]According to the best of our knowledge, there are no studies from Bangladesh evaluating efficacy and safety of alteplaseor other newer thrombolytic agent in patients in acute ischemic stroke. Our centre is one of the largest centres for care and management of patients with acute ischemic stroke in Dhaka, Bangladesh. We have recently started using alteplase for the treatment of acute ischemic stroke and our centre is pioneer in thrombolysis in Bangladesh.

**Material and Methods**

In this retrospective analysis, all patients undergoing thrombolysis for acute ischemic stroke with alteplase from 21 Jan 2018to26 Feb 2019at our centre were included. We did not include patients with acute ischemic stroke who did not undergo thrombolysis. The dose of alteplase in all patients was 0.9 mg/kg. Demographic details, comorbidities, onset to hospital time, onset to needle time and door to needle time were recorded. Effectiveness of alteplase was reported by comparing pre-thrombolysis National Institutes of Health Stroke score (NIHSS) score versus post-thrombolysis NIHSS score. Modified Rankin (mRS) score was also recorded in all patients. Safety and tolerability of alteplase was evaluated by recording adverse events.

**Results**

A total of 10 patients with acute ischemic stroke thrombolysed with alreplase were included in the analysis. Our case series included 6(60%) male patients and 4(40%) female patients. The mean age of patients was 63.8 years. The minimum and maximum age of patient in our case series was 38 years and 84 years respectively (Table 1). Hypertension, diabetes and ischemic heart disease was present in 7(70%), 5(50%) and 2(20%) cases. Atrial fibrillation, Parkinson's disease and dementia, old stroke 1(10%), chronic kidney disease and hypertrophic cardiomyopathy was present in 1(10%) patients each (Table 1). The mean onset to hospital time was 83 (range 0-150) minutes whereas mean onset to needle time was 187(range 75-240) minutes. The mean door to needle time in our case series was 104(range 40-195) minutes (Table 1).

**Table 1:** Details of the cases

| SL No | Age | Gender | Hypertension | Diabetes | Other | Onset to hospital (min) | Onset to needle (min) | Door to needle (min) | Pre TPA NIHSS | Post TPA NIHSS | mRS |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 75 | F | Yes | No | AF | 90 | 220 | 130 | 18 | 15 | 3 |
| 2 | 63 | M | No | No | IHD, HCM | 00 | 75 | 75 | 140 | 0 | 0 |
| 3 | 75 | F | No | Yes | PD, Dementia | 90 | 240 | 150 | 28 | 25 | 6 |
| 4 | 55 | M | No | Yes | IHD | 60 | 180 | 120 | 20 | 14 | 6 |
| 5 | 38 | M | Yes | No | No | 105 | 200 | 95 | 7 | 3 | 0 |
| 6 | 70 | F | Yes | Yes | No | 30 | 225 | 195 | 4 | 1 | 1 |
| 7 | 76 | M | Yes | Yes | CKD | 70 | 130 | 60 | 11 | 9 | 2 |
| 8 | 50 | M | Yes | No | Old stroke | 105 | 230 | 125 | 13 | 9 | 3 |
| 9 | 84 | F | Yes | Yes | No | 150 | 200 | 50 | 13 | 11 | 5 |
| 10 | 52 | M | Yes | No | No | 130 | 170 | 40 | 4 | 1 | 0 |

AF: Atrial fibrillation, CKD: Chronic kidney disease, HCM: Hypertrophic cardiomyopathyIHD: Ischemic heart disease, mRS: Modified Rankin Score, NIHSS: National Institutes of Health Stroke score, PD: Parkinson's disease, TPA: Tissue plasminogen activator

The mean National Institutes of Health Stroke score (NIHSS) score before thrombolysis was 25.8 which decreased to 8.8 after thrombolysis. The reduction in NIHSS score was statistically significant ($p<0.05$; Figure II). The mean modified Rankin score was 2.9 (range 0-6). A total of 4 patients had MRS score between 0 to 1, whereas 3 (30%) had score between 2 to 3. Other 1 and 2 patients had MRS score between 4 to 5 and 6 respectively. Five (50%) patients had MRS score between 0 to 2.

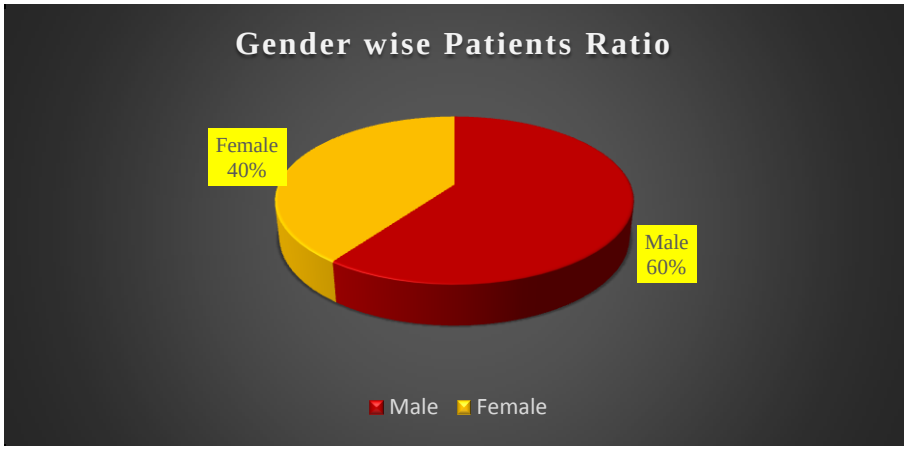


**Figure I:** Gender wise Patients Ratio

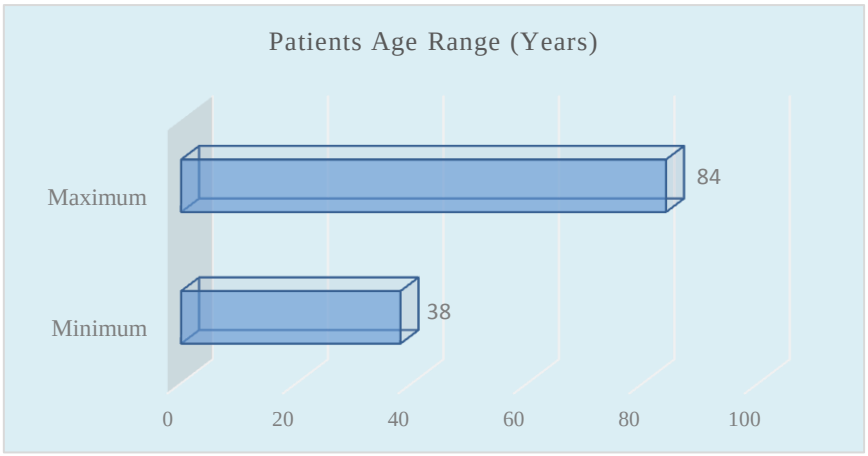


**Figure II:** Patients Age Range (Years)

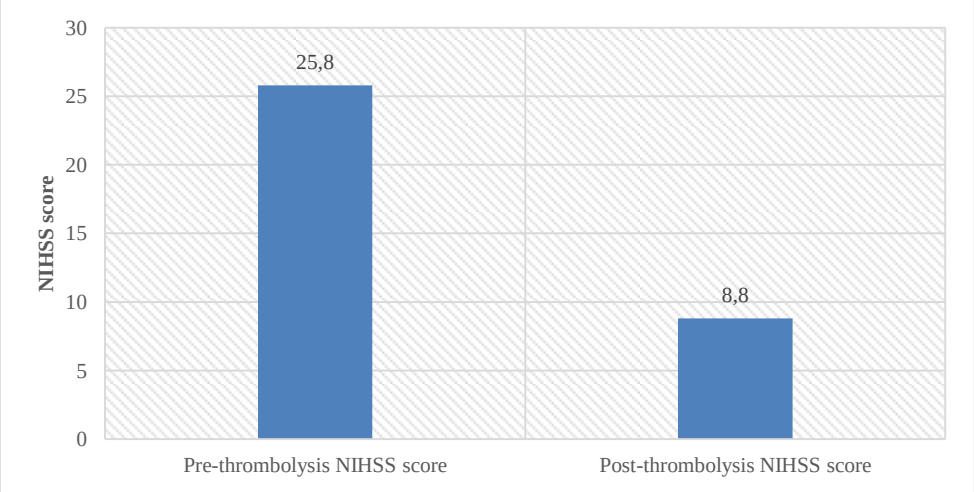


**Figure III:** NIHSS score before and after thrombolysis with Alteplase

*NIHSS: National Institutes of Health Stroke score,

A 75 years old female patient presented to our hospital with right hemiparesis, facial droop and aphasia. She had history of hypertension and atrial fibrillation. The symptoms had started at 1.30 pm whereas she reached hospital at 3 pm. Her NIHSS score before administration of alteplase (at 4 pm) was 18. Alteplase was administered in the standard dose of 0.9 mg/kg at 6 pm. Post-alteplase administration, NIHSS score decreased to 15. The radio-imaging performed at day 0 was compared with that on day 2 (Figure IV).

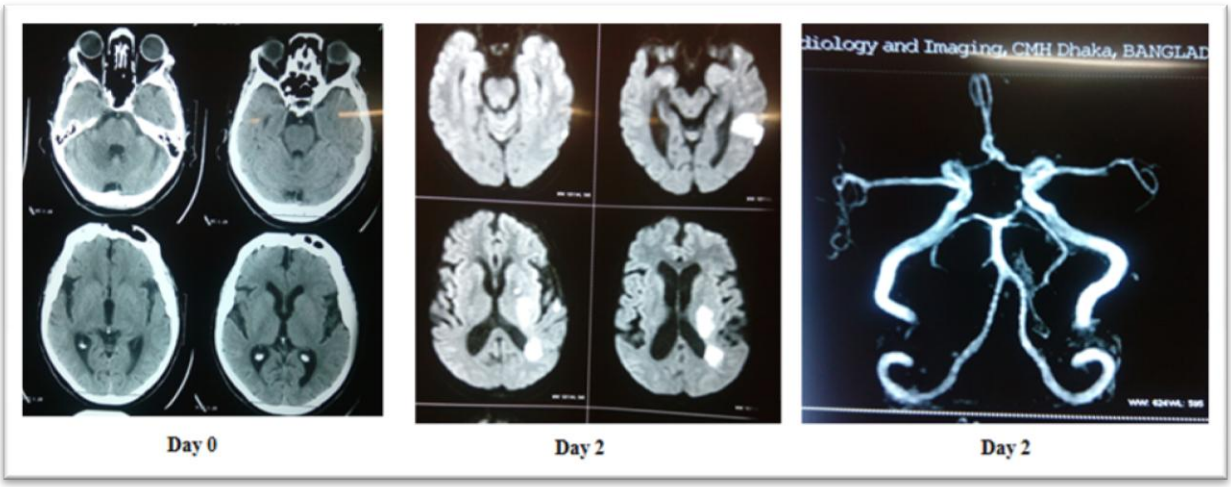


**Figure IV:** Radio-imaging of a 75-year female patient with acute ischemic stroke

Alteplase was well tolerated without any serious adverse events. One patient died due to infection which was not related to alteplase.

**Discussion**

Thrombolysis is the treatment of choice for patients with acute ischemic stroke if patient presents to hospital within recommended window period. However, the ground reality is different. A study from Egypt has reported several barriers for the use of thrombolysis in patients with acute ischemic stroke. Patient related reported barriers include unawareness about stroke, stroke occurrences during sleep, long time required for travel to the hospital resulting in prolonged door-to needle time, cost constraints, fear of side effects. Hospital/clinician related challenges include inadequate number of neurologists and/or bead in the hospital.[15]In Bangladesh also most of these barriers contribute to the lower rates of thrombolysis. Our centre is pioneer in initiating thrombolysis in Dhaka, Bangladesh. We have

recently started using alteplase for thrombolysis in acute ischemic stroke. In this article we presented our results of thrombolysis with alteplase in patients with acute ischemic stroke. A study from Bangladesh reported 49 years of mean age of stroke patients treated at rehabilitation centre.[4]In our case series, minimum age of the patient was 38 years whereas maximum age was 84 years. A study from Beijing, China[16] reported higher standardized prevalence of stroke in males as compared to females. A study from Bangladesh evaluating profile at rehabilitation centre had 77.7% male patients.[4]In our case series too number of males was more than females. It is difficult to generalize the statement for Bangladesh from this study, because number of very small number of cases and this is not a prevalence study. Presence of comorbidities is very common in patients with stroke. A study[16] has reported hypertension (80.7%) to be the most common comorbidity in these patients. Our results are similar to this study and another study from Bangladesh.[4]In our study, 7 (70%) out of 10 patients had hypertension. In a study from Bangladesh[4] evaluating profile of stroke patients treated at rehabilitation centre, 85% patients had history of hypertension before occurrence of stroke. Diabetes mellitus was much more common in patients with stroke our study as compared to another published study[16] (50% vs 16.9%) but less than a study from Bangladesh (77% vs 50%).[4] These comorbidities underline the importance of lifestyle changes for reduce the occurrence of stroke. Control of chronic diseases at their early stages may be useful to reduce the burden of stroke.Safety of TPA is one of the reported concerns for use in routine clinical practice of acute ischemic stroke treatment.[17]Higher age is a risk factor for symptomatic haemorrhageafter administration of r-TPA.[18] In our study, 5 out of 10 patients were more than 65 years of age and all tolerated alteplase well. Male gender, diabetes and uncontrolled hypertension are also known risk factors for symptomatic haemorrhage.[18]In our study, all these patients tolerated alteplase without any complication. The risk of symptomatic intracranial hemorrhage with r-TPA activator is also high in patients taking antiplatelet agents.[19]In our case series, alteplase was well tolerated in all patients. One patient died in the intensive care unit because of infection. However, infection was un-related to alteplase. There were no alteplase related adverse events in the study. There are limited data on use of thrombolytic agent in the treatment of stroke in middle or low income countries.[20] Our case series adds significant knowledge to the quantum of literature on management of stroke in Bangladesh. This is probably first case series reporting successful use of thrombolytic agent in the management of acute ischemic stroke in Bangladesh. Time is an essence in the treatment of acute ischemic stroke especially for administration of thrombolytic agent. Earlier administration of thrombolytic agent results in higher benefits.[21] In a study from North India only 20% patients came within the window period of 4.5 hours, of whom just 4.5% were eligible for thrombolysis. The rate of actual thrombolysis was 3.6%.[20] The mean onset to hospital time in our study was almost similar to a study from North India (83vs 76.8 minutes), but mean door to needle time in our case series was slightly longer (104 vs90 min).[20]A pooled analysis of nine trials showed intravenous alteplase when started within 4.5 hours of stroke onset improves the chance of better functioning.[21] Mean onset to needle time in our study was 187minutes i.e. close to 4.5 hours. In another study from India, the mean onset to needle time in was 177.2 minutes.[22] Optimizing in-hospital stroke treatment with ABC (acute brain care) protocol has been shown to useful in reducing door to needle time.[23]Use of "Stroke code" can also be useful for improving the rates of thrombolysis. A study from Pune, India has shown that implementation of "Stroke code" can be useful to improve rate of thrombolysis in patients with acute ischemic stroke and reduce door to needle time.[24]The authors reported improvement of thrombolysis from 29.7% pre-stroke code period to 44.52% post-stroke code

implementation.[24] At the physician level the challenges include maintenance of blood pressure in recommended range, patient counselling for acceptance of thrombolytic agent and management of hypersensitivity reaction and bleeding in case it occurs. Managing standard door to needle time needs improvement of awareness about symptoms of stroke and reporting to the hospital at the earliest and importance of timely use of thrombolytic agent among hospital staff.Modified Rankin Scale (mRS) score of 0–1 is considered as good outcome.[19]Score of less than or equal to 2 is also considered as favorable outcome. [21]In our study 5(50%) patients acheived MRS score of 2 or less. Considering small number of patients our observations needs careful interpretation. Based on encouraging results, we recommend EMS pre-notification of hospitals, activating the stroke arrival team with a single call, stroke-team-based approach rapid acquisition and interpretation of brain imaging, use of specific protocols and tools, premixing r-TPA, and rapid feedback. Larger studies are required to confirm our observations.

**Conclusion**

In our case series, standard dose of alteplase (0.9 mg/kg) as thrombolytic agent was found to be effective in improvement of NIHSS score without risk of bleeding or other serious adverse events.

**References**


1. GBD 2016 Stroke Collaborators. Global, regional, and national burden of stroke, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol2019; 18: 439–58
2. Islam MN, Moniruzzaman M, Khalil MI, Basri R, Alam MK, Loo KW. Burden of stroke in Bangladesh. Int J Stroke 2013; 8:211-3
3. Katan M, Luft A. Global burden of stroke. SeminNeurol2018; 38:208-11
4. Mamin FA, Islam MS, Rumana FS, Faruqui F. Profle of stroke patients treated at a rehabilitation centre in Bangladesh. BMC Res Notes 2017; 10:520
5. Giang KW, Mandalenakis Z, Nielsen S, Bjorck L, Lappas G, Adiels M, et al. Long-term trends in the prevalence of patients hospitalized with ischemic stroke from 1995 to 2010 in Sweden. PLoS ONE 2017;12: e0179658
6. Feigin VL, Florouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. Lancet. 2014; 383: 245–254
7. Rha JH, Saver JL. The impact of recanalization on ischemic stroke outcome: a meta-analysis. Stroke 2007; 38:967-73
8. Kassem-Moussa H, Graffagnino C. Nonocclusion and spontaneous recanalization rates in acute ischemic stroke: a review of cerebral angiography studies. Arch Neurol2002; 59:1870-3
9. Fugate JE, Rabinstein AA. Absolute and relative contraindications to IV rt-PA for acute ischemic stroke. The Neurohospitalist2015; 5:110-21
10. Dhillon S. Alteplase: a review of its use in the management of acute ischaemic stroke. CNS Drugs 2012; 26:899-926
11. Syalaja PN, Dong W, Grotta JC, Miller MK, Tomita K, Hamilton S, et al. Safety outcomes of alteplase among acute ischemic stroke patients with special characteristics. Neurocrit Care 2007; 6:181-5
12. Anderson CS, Robinson T, Lindley RI, Arima H, Lavados PM, Lee TH, et al. Low-dose versus standard-dose intravenous alteplase in acute ischemic stroke. N Engl J Med 2016; 374:2313-23
13. Chao AC, Han K, Lin SF, Lin RT, Chen CH, Chan L, et al. Low-dose versus standard-dose intravenous alteplase for octogenerian acute ischemic stroke

patients: A multicenter prospective cohort study. J NeurolSci2019; 399:76-81
14. Yamaguchi T, Mori E, Minematsu K, Nakagawara J, Hashi K, Saito I, et al. Alteplase at 0.6 mg/kg for acute ischemic stroke within 3 hours of onset: Japan Alteplase Clinical Trial (J-ACT). Stroke 2006; 37:1810-5
15. Bahnasy WS, Ragab OAA, Elhassanien ME. Stroke onset to needle delay: Where these golden hours are lost? An Egyptian center experience. eNeurologicalSci 2019;14: 68–71
16. Ma AJ, Dong Z, Li G. Prevalence rates and risk factors on stroke among 50 - 79 years-olds in Beijing, 2011. Zhonghua Liu Xing Bing XueZaZhi2012; 33:645-8
17. Micieli G, Marcheselli S, Tosi PA. Safety and efficacy of alteplase in the treatment of acute ischemic stroke. Vac Health Risk Manag2009; 5:397-409Owais M, Panwar A, Valupadas C, Veeramalla M. Acute ischemic stroke thrombolysis with tenecteplase: an institutional experience from South India. Ann Afr Med 2018; 17:90-3
18. Miller DJ, Simpson JR, Silver B. Safety of thrombolysis in acute ischemic stroke: A review of complications, risk factors, and newer technologies. The Neurohospitalist 2011; 1:138-147
19. Lindley RI, Wardlaw JM, Whiteley WN, Cohen G, Blackwell L, Murray GD, et al. Alteplase for acute ischemic stroke: outcomes by clinically important subgroups in the Third International Stroke Trial. Stroke 2015; 46:746-56
20. William AG, Pannu A, Kate MP, Jaison V, Gupta L, Bose S, et al. Quality indicators of intravenous thrombolysis from North India. Ann Indian AcadNeurol2017; 20:393-98.
21. Lees KR, Emberson J, Blackwell L, Bluhmki E, Davis SM, Donnan GA, et al. Effects of alteplase for acute stroke on the distribution of functional outcomes: a pooled analysis of nine trials. Stroke. 2016; 47: 2373–2379
22. Mehta A, Mahale R, Buddaraju K, Majeed A, Sharma S, Javali M, *et al*. Intravenous thrombolysis for acute ischemic stroke: Review of 97 patients. J Neurosci Rural Pract2017; 8:38-43
23. Zinkstok SM, Beenen LF, Luitse JS, Majoie CB, Nederkoorn PJ, Roos YB. Thrombolysis in Stroke within 30 Minutes: Results of the Acute Brain Care Intervention Study. PLoS ONE 2016;11: e0166668. doi:10.1371/journal. pone.0166668
24. Gurav SK, Zirpe KG, Wadia RS, Naniwadekar A, Pote PU, Tungenwar A, et al. Impact of "Stroke Code"-rapid response team: An Attempt to Improve Intravenous Thrombolysis Rate and to Shorten Door-to-Needle Time in Acute Ischemic Stroke. Indian J Crit Care Med 2018; 22:243-48.