Original Article

The need for a population-based, dose optimization study for recombinant tissue plasminogen activator in acute ischemic stroke: A study from a tertiary care teaching hospital from South India

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Abstract

Context: The guideline recommended dose of intravenous (i.v) recombinant tissue-type plasminogen activator (rt-PA) for acute ischemic stroke is 0.9 mg/kg in the European and American populations. In Asiatic population, some studies have shown that a lower dose of i.v rt-PA is equally efficacious. **Aims:** To assess if there is a need for a dose optimization for i.v rt-PA study among Indians. **Setting and Design:** A prospective, observational database of acute stroke cases that presented to a tertiary care institute over a period of 1 year was made. **Methods:** The data procured using a prestructured elaborate pro forma. Based on the dose of rt-PA received, the individuals were divided into three groups; Group 1 (0.6–0.7 mg/kg), Group 2 (0.7–0.8 mg/kg), and Group 3 (0.8–0.9 mg/kg). Improvement was assessed in each group and between the thrombolysed and nonthrombolysed individuals. **Statistical Analysis Used:** The nonparametric Mann–Whitney U-test (Wilcoxon rank-sum test) was applied for assessing improvement of National Institutes of Health Stroke Scale score with significance level of $\alpha < 0.05$ ($P < 0.012$) and compliance level at 95%. **Results:** Between the thrombolysed ($n = 46$) and nonthrombolysed ($n = 113$) group, there was a statistically significant neurological improvement in the thrombolysed group. Clinical improvement was noted in 75%, 85.7%, and 66.7% of individuals receiving rt-PA in Groups 1, 2, and 3, respectively. Four out of the five who developed a clinically significant intracranial hemorrhage were thrombolysed at a dose of 0.8–0.9 mg/kg rt-PA (Group 3). **Conclusion:** There is a need for a properly randomized, dose optimization study of i.v rt-PA in the Indian subcontinent.

Key Words

Acute ischemic stroke, dose optimization, India, recombinant tissue-plasminogen activator, thrombolysis

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Introduction

Variable dose regimens of intravenous (i.v) recombinant tissue-plasminogen activator (rt-PA) are used across Asia without any reliable or established evidence.[1] The guideline recommended dose of i.v rt-PA for acute ischemic stroke is 0.9 mg/kg in the European and American populations.[2] In Asiatic population, some studies have shown that a lower dose of rt-PA is equally efficacious.[3] In China, a study of the different doses of rt-PA for acute stroke concluded that they

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did not support the dose of 0.9 mg/kg being optimal for all patients in the East Asian population.[4] Another study in acute ischemic stroke patients in China demonstrated that i.v rt-PA regimen, 0.9 mg/kg, with a maximum dose of 50 mg had a favorable outcome.[5]

Our study was conducted at a single tertiary care institute, where the institutional policy is to administer a maximum dose of 50 mg of rt-PA. The rationale behind this dosing is that, Asian studies have shown that low-dose i.v rt-PA is equally efficacious as the standard dose (0.9 mg/kg).[4-6] The evidence for the rationalization among the Indian population is minimal, which warrants further research. The fact that this is a more financially feasible option for individuals where the health-care expenditure of the average Indian is mostly out of one's own pocket (OOP)[7] also plays an important part in the country.

Methods

A prospective, observational database of acute stroke cases that presented to a tertiary care institute over a period of 1 year was made after approval from the Institutes Research Board and Ethics Committee. The data were procured using an elaborate prestructured pro forma. This included the clinco-bio-ethno-geographical data of the individuals, their serial National Institutes of Health Stroke Scale (NIHSS) score for 7 days, and modified Rankin Score (mRS) for every hospital visit till the end of 3 years.[8] It was noted that the dosage of rt-PA used in this institute was a maximum of 50 mg. This led to the research question whether the dose of rt-PA used was adequate in the individuals.

For the purpose of this study, the efficacy end-point assessed was the neurological improvement at 7 days and safety end-points were clinically significant intracerebral hemorrhage (ICH) and death. Improvement in neurological status was defined as a drop in the NIHSS score by 4 or more points or a score of zero at 7 days.[9] The stroke scale was completed by the investigators who were usually unaware of previous scores for an individual patient. Functional outcome of the individuals was followed up for 3 years. In the event, they did not show up for a follow-up; they were telephonically interviewed and mRS scored.

Descriptive and inferential statistical analyses were carried out in the present study. The statistical software namely IBM, SPSS 22.0, R environment version 3.1.1 was used for the analysis of the data. The results of categorical measurements are presented in number (%). The nonparametric Mann–Whitney U-test (Wilcoxon rank-sum test) was applied for assessing for improvement of NIHSS score among the thrombolysed and nonthrombolysed individuals with significance level of $\alpha < 0.05$ ($P < 0.012$) and compliance level at 95%.

Based on the dose of rt-PA received, the individuals were divided into three groups.

Group 1 (0.6–0.7 mg/kg), Group 2 (0.7–0.8 mg/kg), and Group 3 (0.8–0.9 mg/kg), and improvement was assessed in each group [Figure 1].

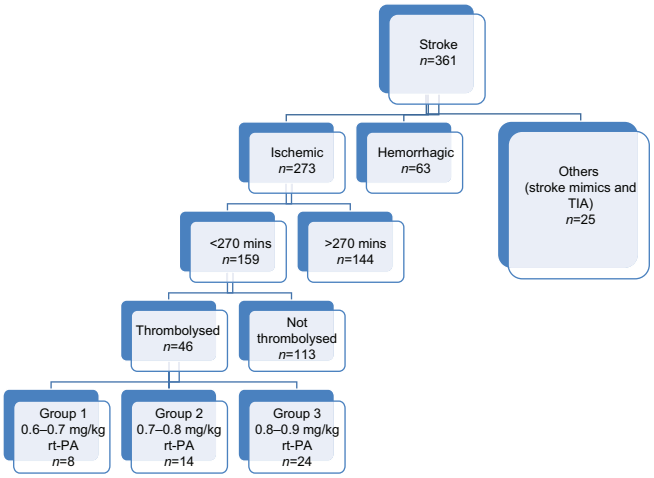

Figure 1: Flow Chart: Stratifying suspected stroke patients

Results

Three hundred and sixty-one clinically suspected stroke patients presented to the emergency department of the institute, of which 229 (63.4%) reached within 270 min of onset of symptoms. One hundred and fifty-nine of the 229 had an ischemic stroke [Figure 1]. Sixty-two of the 159 were thrombolytic candidates, but only 46 got thrombolysed. This was because 11 (17.7%) could not afford the treatment and five declined consent due to fear of risk of hemorrhage.

When the thrombolysed ($n = 46$) and nonthrombolysed ($n = 113$) group were compared, it was noted that there was a statistically significant neurological improvement in the thrombolysed group ($P < 0.012$) [Figure 2].

73.9% (34/46) patients in the thrombolysed group had improvement, whereas among the nonthrombolysed individuals, 45.1% improved (51/113).

The weight of the patients was charted; subgroups were created based on the dose of rt-PA received and analyzed.

Five individuals who underwent thrombolysis developed a clinically significant intracranial hemorrhage (ICH) postthrombolysis. Four of those who developed a clinically significant ICH were thrombolysed at a dose of 0.8–0.9 mg/kg rt-PA and one at 0.6–0.7 mg/kg.

Six individuals passed away within 7 days of thrombolysis of which four deaths were due to ICH, one had a very large ischemic stroke, and one had an airway accident [Table 1]. Clinical improvement was noted in 75%, 85.7%, and 66.7% of the patients in the three groups, respectively [Table 2]. The thrombolysed candidates ($n = 46$) were followed up, and at the end of 3 years, eight (17.4%) were dead [Table 1], 19 (41.3%) had functionally good outcome with mRS of ≤1, no improvement was seen in six (13%), whereas 13 (28.3%) were lost to follow-up [Table 3]. Fifty percent of the individuals in Group 2, whereas 41.7% of the individuals in Group 3 had a functionally good outcome.

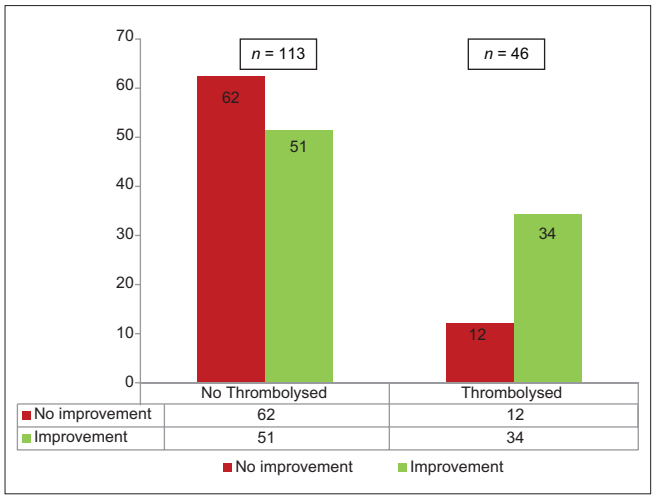

Figure 2: 7 day National Institutes of Health Stroke Scale improvement[a] postlysis

Null hypothesis	Test	Significant	Decision
The distribution of '7 day NIHSS improvement' is the same across categories of thrombolysis (thrombolysed and not thrombolysed)	Independent-sample Mann-Whitney U test	0.012	Reject the hypothesis

The significance level is 0.05. [a]defined as NIHSS improvement by 4 points or more or a score of 0 at 7 days. The independent sample non parametric Mann-Whitney U test (Wilcoxon rank-sum test) was applied and we find that the asymptotic significance with p value 0.012 in '7 day NIHSS improvement' across categories of patients presenting to the ED within 270 minutes-. So we reject the null hypothesis with significance level of α <0.05 (*P*<0.012) and compliance level at 95%. 73.9%(34/46) patients whereas in the non thrombolysed individuals 45.1% improved (51/113)

Discussion

Thrombolytics in stroke is a relatively newer tool in the armamentarium, of a neurologist and emergency physician. rt-PA has been approved in the United States for treatment of acute ischemic stroke since 1996.[10]

Many controlled trials have demonstrated that thrombolysis with rt-PA is an effective treatment for acute stroke if given within first 3 h of onset of symptoms.[11,12]

Subsequent research has confirmed benefits of rt-PA when used up to 4½ h after the onset of ischemic stroke.[12]

The standard dose of i.v rt-PA was determined after two pilot open-labeled studies.[13,14] In the phase 1 pilot study, 74 patients were treated within 90 min of symptom onset over seven dose tiers of tissue plasminogen activator, ranging from 0.35 mg/kg to 1.08 mg/kg, and it was noted that intracranial hematoma did not occur in any of the 58 patients treated with <0.85 mg/kg.[13] A low-dose rt-PA (0.6 mg/kg) is the standard approved treatment for acute ischemic stroke in Japan after conducting many studies.[15-17] No such trials have been conducted among the Indian population.

Table 1: Mortality data

Mortality data	Mortality		Total in each group
	at 7 days	at 3 years	
Group 1			
Count	2	2	8
Percentage within groups	25.0	25.0	
Group 2			
Count	0	2	14
Percentage within groups	0.0	14.3	
Group 3			
Count	4	4	24
Percentage within groups	16.7	16.7	
Total			
Count	6	8	46
Percentage within groups	13.0	17.4	

Six individuals (13%) passed away within 7 days of thrombolysis. Whereas at the end of 3 years, eight (17.4%) were dead. At the end of 7 days, mortality was 25%, 0%, and 16.7%; in Groups 1, 2, and 3, respectively. At the end of 3 years, mortality was 25% 14.3%, and 16.7% in Groups 1, 2, and 3, respectively. Mortality was least in Group 2 (0.7-0.8 mg/kg)

Table 2: 7 days National Institutes of Health Stroke Scale improvement across groups

7 days improvement across groups	improvement	Total in each group
Group 1		
Count	6	8
Percentage within groups	75.0	
Group 2		
Count	12	14
Percentage within groups	85.7	
Group 3		
Count	16	24
Percentage within groups	66.7	
Total		
Count	34	46
Percentage within groups	73.9	100.0

At the end of 7 days, 75%, 85.7%, 66.7% improved, respectively, in Groups 1, 2 and 3. Highest percentage of improvement was seen in Group 2 and least in Group 3

In our study, higher percentage of bleed and lesser clinical improvement were seen in the 0.8–0.9 mg/kg group compared to lower dose (0.7–0.8 mg/kg) group. The Taiwan Thrombolytic Therapy for Acute Ischemic Stroke study group compared low dose (0.65–0.79 mg/kg) and standard dose (0.88–0.92 mg/kg) of rt-PA in Chinese patients and their data showed that symptomatic ICH and mortality were higher in the standard-dose group.[18] There are different hypotheses put forward to explain this rationale. Studies have observed that there is a racial difference in sensitivity to rt-PA. Dark-skinned patients have been shown to have an enhanced sensitivity to rt-PA in patients with acute coronary syndrome.[19] The Japanese when compared to the Americans have been shown to have a higher concentration of plasma fibrinogen and fibrinogen activator inhibitor levels.[20] India is a melting pot of various races[21] and whether racial differences attribute to this varied response is yet to be studied among stroke victims in the Indian subcontinent.

Table 3: Follow-up data at the end of 3 years

Groups	3rd year follow-up			
	Dead	Functionally good outcome mRS ≤1	Lost follow up	No improvement
Group 1				
Count	2	2	2	2
Percentage within groups	25.0	25.0	25.0	25.0
Group 2				
Count	2	7	3	2
Percentage within groups	14.3	50.0	21.4	14.3
Group 3				
Count	4	10	8	2
Percentage within groups	16.7	41.7	33.3	8.3
Total				
Count	8	19	13	6
Percentage within groups	17.4	41.3	28.3	13.0

At the end of 3 years, 25%, 50%, and 41.7% in Groups 1, 2, and 3, respectively, had mRS ≤1 (functionally good outcome). mRS = Modified Rankin Score

In our study, improvement was seen in a higher percentage of individuals receiving lower dose of thrombolytic agent −0.7–0.8 mg/kg rather than the internationally recommended 0.9 mg/kg [Table 2]. It should be noted that this was not a statistically significant difference since the number of patients studied in each group was very low, but the noninferiority *per se* points out the necessity for further research on the subject.

About 17.7% of the individuals in this study could not afford the treatment modality in this urban tertiary care institute. In rural India, this number would be even more high. Lack of access to stroke care, financial constraints, and lack of infrastructure are of concern in developing nations.[22-24] In India, rt-PA is available as 50 mg vials and 20 mg vials. A vial of 50 mg of the thrombolytic agent costs Rs. 40000 (594US$) which is almost double the monthly wages of a middle-class adult in India and this makes thrombolysis inaccessible to most were the health care expenditure is out of OOP.[7,25]

Fifty milligrams vial at 0.9 mg/kg would be sufficient to treat only someone up to the weight of 55.6 kg. Anything more than that would warrant additional vials of rt-PA which would add to the financial burden. A lower dose of thrombolytic agent, for instance 0.6 mg/kg, would mean that 50 mg vial would benefit an adult up to 83.3 kg, which, in the Indian subcontinent, would also be more affordable, making the option more accessible. If proven to be more efficacious or even noninferior than the regular 0.9 mg/kg dose, there would be significant financial gain for the patient, health-care providers including doctors, and stroke treatment government facilities responsible for health care. It is evident that further studies are needed in the subcontinent to optimize the dose required for the treatment of individuals.

Limitations

Although the database was made prospectively, the research question and subgroup formulation were done retrospectively. There was no proper randomization of the thrombolysed groups, and at the end of 3 years, 28% were lost to follow-up. Although all clinically suspected stroke cases (n = 361) were included in formulating the database, the thrombolysed limb constituted only a very small size (n = 46). The number in each individual subgroup was therefore too small to provide any statistically significant conclusion with regard to an optimal dose. It should also be noted that this study was done at a single center, and whether this is applicable in other parts of the country also needs to be further studied.

Conclusion

There are no proper randomized trials of rt-PA among the Indian population to date.

There exists a considerable variation in the dose of rt-PA in recent publications from Asia.

Although the low sample (n = 46), poorly randomized groups, studied in a single tertiary care teaching institute in South India, minimizes the scope for clinical translation of this research to clinical work, it does point toward the need for further research on dose optimization of i.v rt-PA in the Indian population.

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Conflicts of interest

There are no conflicts of interest.

References

1. Sharma VK, Ng KW, Venketasubramanian N, Saqqur M, Teoh HL, Kaul S, *et al.* Current status of intravenous thrombolysis for acute ischemic stroke in Asia. Int J Stroke 2011;6:523-30.
2. Powers WJ, Derdeyn CP, Biller J, Coffey CS, Hoh BL, Jauch EC, *et al.* 2015 American Heart Association/American Stroke Association focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2015;46:3020-35.
3. Eissa A, Krass I, Bajorek BV. Optimizing the management of acute ischaemic stroke: A review of the utilization of intravenous recombinant tissue plasminogen activator (tPA). J Clin Pharm Ther 2012;37:620-9.
4. Chao AC, Liu CK, Chen CH, Lin HJ, Liu CH, Jeng JS, *et al.* Different doses of recombinant tissue-type plasminogen activator for acute stroke in Chinese patients. Stroke 2014;45:2359-65.
5. Pan SM, Liu JF, Liu M, Shen S, Li HJ, Dai LH, *et al.* Efficacy and safety of a modified intravenous recombinant tissue plasminogen activator regimen in Chinese patients with acute ischemic stroke. J Stroke Cerebrovasc Dis 2013;22:690-3.
6. Huang Y, Sharma VK, Robinson T, Lindley RI, Chen X, Kim JS, *et al.* Rationale, design, and progress of the ENhanced Control of Hypertension ANd Thrombolysis strokE stuDy (ENCHANTED) trial: An international multicenter 2×2 quasi-factorial randomized controlled trial of low-vs. standard-dose rt-PA and early intensive vs. guideline-recommended blood pressure lowering in patients with acute ischaemic stroke eligible for thrombolysis treatment. Int J Stroke 2015;10:778-88.
7. Ahlin T, Nichter M, Pillai G. Health insurance in India: What do we know and why is ethnographic research needed. Anthropol Med 2016;23:102-24.

8. Brott T, Adams HP Jr., Olinger CP, Marler JR, Barsan WG, Biller J, *et al.* Measurements of acute cerebral infarction: A clinical examination scale. Stroke 1989;20:864-70.
9. Kerr DM, Fulton RL, Lees KR; VISTA Collaborators. Seven-day NIHSS is a sensitive outcome measure for exploratory clinical trials in acute stroke: Evidence from the Virtual International Stroke Trials Archive. Stroke 2012;43:1401-3.
10. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. N Engl J Med 1995;333:1581-7.
11. Jauch EC, Saver JL, Adams HP Jr., Bruno A, Connors JJ, Demaerschalk BM, *et al.* Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44:870-947.
12. Wardlaw JM, Murray V, Berge E, del Zoppo GJ. Thrombolysis for acute ischemic stroke, update August 2014. Stroke 2014;45:e222-5.
13. Brott TG, Haley EC Jr., Levy DE, Barsan W, Broderick J, Sheppard GL, *et al.* Urgent therapy for stroke. Part I. Pilot study of tissue plasminogen activator administered within 90 minutes. Stroke 1992;23:632-40.
14. Haley EC Jr., Levy DE, Brott TG, Sheppard GL, Wong MC, Kongable GL, *et al.* Urgent therapy for stroke. Part II. Pilot study of tissue plasminogen activator administered 91-180 minutes from onset. Stroke 1992;23:641-5.
15. Mori E, Yoneda Y, Tabuchi M, Yoshida T, Ohkawa S, Ohsumi Y, *et al.* Intravenous recombinant tissue plasminogen activator in acute carotid artery territory stroke. Neurology 1992;42:976-82.
16. 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.
17. Mori E, Minematsu K, Nakagawara J, Yamaguchi T, Sasaki M, Hirano T; Japan Alteplase Clinical Trial II Group. Effects of 0.6 mg/kg intravenous alteplase on vascular and clinical outcomes in middle cerebral artery occlusion: Japan Alteplase Clinical Trial II (J-ACT II). Stroke 2010;41:461-5.
18. Chao AC, Hsu HY, Chung CP, Liu CH, Chen CH, Teng MM, *et al.* Outcomes of thrombolytic therapy for acute ischemic stroke in Chinese patients: The Taiwan Thrombolytic Therapy for Acute Ischemic Stroke (TTT-AIS) study. Stroke 2010;41:885-90.
19. Sane DC, Stump DC, Topol EJ, Sigmon KN, Clair WK, Kereiakes DJ, *et al.* Racial differences in responses to thrombolytic therapy with recombinant tissue-type plasminogen activator. Increased fibrin (ogen) olysis in blacks. The Thrombolysis and Angioplasty in Myocardial Infarction Study Group. Circulation 1991;83:170-5.
20. Iso H, Folsom AR, Sato S, Wu KK, Shimamoto T, Koike K, *et al.* Plasma fibrinogen and its correlates in Japanese and US population samples. Arterioscler Thromb Vasc Biol 1993;13:783-90.
21. Majumder PP. People of India: Biological diversity and affinities. Evolutionary Anthropology: Issues, News, and Reviews; 1998:100-10.
22. Nandigam K, Narayan SK, Elangovan S, Dutta TK, Sethuraman KR, Das AK. Feasibility of acute thrombolytic therapy for stroke. Neurol India 2003;51:470-3.
23. Durai Pandian J, Padma V, Vijaya P, Sylaja PN, Murthy JM. Stroke and thrombolysis in developing countries. Int J Stroke 2007;2:17-26.
24. Ghandehari K. Barriers of thrombolysis therapy in developing countries. Stroke Res Treat 2011;2011:686797.
25. Nair D. Determinants of Enrollment in Comprehensive Health Insurance Scheme and Implementation Challenges: A Study in Kerala, South India. Health Science Journal 2016;10:1-6.