

Safety and feasibility of intravenous thrombolytic therapy in Iranian patients with acute ischemic stroke

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Abstract

Background: Thrombolytic therapy is the only approved treatment for acute cerebral ischemia. The hemorrhagic transformation is the greatest complication of this treatment, which may occur after recanalization of occluded artery. The aim of this study was to determine factors associated with clinical improvement and worsening in patients with acute ischemic stroke treated with intravenous thrombolysis.

Methods: Thirty seven patients who were treated with intravenous thrombolysis between August 2010 and August 2012 who had the inclusion criteria were studied. In this prospective study, all of the admitted patients in stroke unit, monitored for at least 48 hours. We registered all patients' information in a stroke data registry and followed them for at least 6 months.

Results: Thirty seven patients with acute ischemic stroke who treated with recombinant tissue plasminogen activator (r-TPA) were studied. There were hemorrhagic transformations in 9 (24%) patients. Seven of them (18%) revealed intracerebral hemorrhages (ICH) within the control brain CT after 24 hours without any deterioration of neurologic symptoms (asymptomatic ICH). Although outcomes of patients with symptomatic post r-TPA hemorrhages were worse than non-hemorrhagic post r-TPA patients, there were no significant differences between asymptomatic post r-TPA hemorrhages and non-hemorrhagic post r-TPA patients, according to the National Institutes of Health Stroke Scale (NIHSS) at admission ($p = 0.2$), after 24 hours ($p = 0.07$) and after 7 days ($p = 0.06$) post treatment.

Conclusion: If the r-TPA protocol is followed carefully, the risk of symptomatic hemorrhage is low (about 7%). Taking r-TPA was feasible and safe in our study population; thus, it can be applied for other Iranian patients.

Keywords: Stroke, Thrombolytic Therapy, Iran.

Introduction

Stroke is an important cause of death and disability in the world. The major causes of ischemic strokes are occlusion of cerebral arteries either by a cardiac embolus or by thrombus formation in atherosclerotic vessel walls. The process of thrombus formation is initiated by two separate but interacting mechanisms: fibrin formation and platelet activation. Thrombolytic therapy is the only approved treatment for acute cere-

bral ischemia in order to recanalize the occluded artery and reestablish the blood flow (1). However, benefit from this treatment rapidly declines over time after symptom onset. The number needed to treat to have one patient with favorable outcome is 4-5 treatment started within 90 minutes after symptom onset (2). This number increases to 14 if the treatment has been started between 3 to 4.5 hours after symptom onset (2,3). Within this current time window, early recanalisation is strongly associated with

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improved functional outcomes and reduced mortality (4,5). For this purpose the duration of the ischemia should be considered as an important factor of the viability of neurons in the penumbra. There are several reports of good outcomes and recovery after treatment of acute stroke with thrombolytic therapy within 4.5 hours after the onset (6-8).

Today only a small proportion of stroke patients in Iran have the benefit of thrombolytic therapy. The reasons are delaying in referring patients, local unavailability of thrombolytic therapy, fear of hemorrhagic transformation and limited number of existing stroke units. There is scarce data about r-TPA usage in the Middle-East.

The aim of this study was to evaluate the feasibility, outcome and safety of intravenous thrombolysis with r-TPA in acute ischemic stroke patients treated in a university hospital with a unit specialized in early stroke treatment. We evaluated patients transferring and the time interval before starting the treatment. We also studied the effects of hemorrhagic transformation on stroke prognosis. The population studied was patients admitted and treated with intravenous r-TPA during the first two years from implementation of this therapy.

Methods

We prospectively recorded all patients treated with intravenous (IV) r-TPA for ischemic stroke at our hospital between August 2010 and August 2012 in an ongoing register. The protocol was approved by the local ethics committee. All patients with acute ischemic stroke admitted within the first four and half hours of stroke onset were considered for intravenous thrombolytic therapy. Inclusion and exclusion criteria for systemic r-TPA treatment were those of the National Institute of Neurological Disorders and Stroke (NINDS) study. This study was conducted at stroke unit of Firoozgar university hospital, affiliated to Tehran University of medical sciences. Patients who were treated with intravenous thrombolysis between August 2010 and

August 2012 were included in the study. Patients admitted to our hospital with acute stroke were first examined clinically in the emergency room. Brain CT scan was performed as soon as possible and interpreted by an experienced neuro-radiologist. Informed consent was obtained from the patient or his relatives. A total of 37 patients were treated with intravenous r-TPA within 4.5 hours from symptom onset. Intravenous r-TPA (0.9 mg/kg) was prescribed in eligible patients with acute ischemic stroke within 4.5 hours after the onset. The Protocol of r-TPA administration was based on the research supported by the the National Institute of Neurological Disorders and Stroke (NINDS) (9). Patients received 0.9 mg/kg of IV r-TPA (alteplase; ActilyseR), 10% as bolus and 90% as continuous infusion over 60 min, up to a maximum of 90 mg. IV r-TPA was administered immediately after screening and admission to the emergency room or stroke unit.

Most of the exclusion criteria were similar to the guidelines proposed by the American Heart Association and American Stroke Association. We gathered data from the Firoozgar stroke registry. Variables were biographic information of patients, time of arrival to hospital, time of r-TPA administration, dosage of r-TPA, and follow up information. The patients or their family completed a consent form for application of their information in the study. An examination by one neurologist was performed during the hospital stay. A cerebral CT scan was performed before discharge if the neurological status did not improve or immediately if it deteriorated.

Intracerebral hemorrhage (ICH) was categorized primarily as symptomatic versus asymptomatic, based on the NINDS trial. Symptomatic ICH was defined as a CT-documented hemorrhage related to clinical deterioration as judged by the treating physician. Asymptomatic hemorrhagic transformation refers to evidence of post-treatment ICH on T2-weighted MRI or CT without clinical evidence of neurological deterioration, i.e. National Institutes of

Table 1. Comparison of age, r-TPA dosage, mean systolic and diastolic blood pressure, NIHSS, MRS, Barthel score and duration of hospitalization between patients with and without hemorrhagic transformation.

	Patients with hemorrhagic transformation		Patients without hemorrhagic transformation	p-value
	Symptomatic	Asymptomatic		
Mean Age \pm SD (Number patients)	78 \pm 5.9	73.4 \pm 12	69.2 \pm 10.6	
p-value		0.11		0.9
r-TPA dosage \pm SD	72 \pm 2	59.8 \pm 7	63 \pm 14.1	
p-value		0.59		0.09
CVA to r-TPA \pm SD (min)	115 \pm 91	181 \pm 65	176 \pm 59	
p-value		0.1		0.51
Mean SBP \pm SD (mm/Hg)	160 \pm 42.2	152.5 \pm 30.5	156 \pm 29.7	
p-value		0.2		0.09
Mean DBP \pm SD (mm/Hg)	85 \pm 7.7	86.9 \pm 9.6	89 \pm 15.9	
p-value		0.6		0.2
Mean BS \pm SD	142 \pm 19.0	150.8 \pm 60.8	143.7 \pm 37.3	
p-value		0.6		0.6
NIHSS at admission \pm SD	16 \pm 4.2	16.4 \pm 5.5	15.7 \pm 4.3	
p-value		0.9		0.2
NIHSS after 1 day \pm SD	11 \pm 1	13.2 \pm 4.0	13.8 \pm 5.4	
p-value		0.9		0.07
NIHSS after 7 days \pm SD	13 \pm 1	12.8 \pm 2.3	12.5 \pm 5.8	
p-value		0.3		0.06
MRS(sd)	5 \pm 1.8	4.25 \pm 0.9	3.5 \pm 1.3	
p-value		0.9		0.2
Barthel(sd)	18.5 \pm 10.6	15 \pm 25.9	33 \pm 30.8	
p-value		0.4		0.3
Duration of hospitalization (sd) (days)	20.5 \pm 19.0	27 \pm 26.6	12 \pm 9	
p-value		0.5		0.04

MRS (Modified Rankin Scale)

NIHSS (National Institutes of Health Stroke Scale)

Health Stroke Scale (NIHSS) within three points of pre-treatment score. Any deterioration of symptoms or signs was a criterion for performing a Brain CT-scan without contrast for ruling out of hemorrhagic transformation. If there was no deterioration of symptoms or signs, the brain CT was performed after 24 hours of stroke onset to decide on initiation of anti-platelet therapy. In this cross-sectional study, asymptomatic ICH has been considered as

ICH visible on brain CT after 24 hours without any deterioration of symptoms.

Statistical analysis: Patients were classified into three major groups: symptomatic ICH, asymptomatic ICH, and no ICH. Initial bi-variate comparisons were performed among these three groups. The data was expressed as mean \pm standard deviation (SD). Chi-square test and t-test were used for qualitative and quantitative data, respec-

tively. Statistical significance for intergroup differences was assessed by Student's t-test for continuous variables, Mann-Whitney U test for nonparametric data, and Fisher exact test for categorical comparisons. A probability value of <0.05 was regarded as significant. All statistical analyses were performed with SPSS version 16 for windows (SPSS Inc. Chicago, IL, USA).

Results

Thirty seven patients with acute ischemic stroke who treated with r-TPA were evaluated. The mean age of participants was 70.2 ± 10.9 years (range 44 to 87 years). The overall mean NIHSS score before administration of r-TPA was 15.4 ± 4.6 (range 7 to 25). The mean symptom to-needle time was 186 ± 61 minutes (range 50 to 270 minutes).

Thirteen (35.1%) of them were female and 24 (64.9 %) were male. The mean dose of administered r-TPA was 60.5 ± 12.04 mg (50-90 mg). There were hemorrhagic transformations in 9 (24%) patients of which 5 patients were male and 5 were female. Seven (18%) cases of hemorrhagic transformations were found incidentally within 24 hours control brain CT without any deterioration of neurologic symptoms (asymptomatic ICH), one of them had ICH after 48 hours and the other had ICH after 72 hours that were associated with decrement of the level of consciousness (symptomatic ICH). There were no significant differences in r-TPA dosage and CVA (cerebrovascular accident) to r-TPA time between patients with and without hemorrhagic transformation ($p=0.51$). Mean Systolic and diastolic blood pressure was higher in patients with symptomatic hemorrhagic transformation, but this difference was not significant ($p=0.09$).

There were no significant differences between non-hemorrhagic post r-TPA and asymptomatic post r-TPA hemorrhagic outcome and prognosis according to NIHSS, Barthel ($p=0.3$) and MRS (Modified Rankin Scale) ($p=0.2$) scale in the two groups

(Table 1).

There were no significant association between occurrence of symptomatic or asymptomatic hemorrhagic transformation with history of diabetes mellitus ($p= 0.7$), hypertension ($p= 0.9$), atrial fibrillation ($P= 0.3$), previous history of CVA ($p= 0.7$), TIA ($p= 0.6$) and hyperlipidemia ($p= 0.3$). Hospitalization was significantly longer in hemorrhagic group in comparison to non-hemorrhagic group ($p=0.04$).

Discussion

The results of this clinical study suggest that intravenous thrombolytic therapy for ischemic stroke is feasible and safe in a hospital setting in the treatment of acute stroke in Iranian patients. Overall outcome will only be improved when the majority of these patients can be given the benefit of thrombolytic therapy. However, the treatment's safety must be guaranteed by a defined quality of structure, process and outcome. Prior to introduction of intravenous thrombolysis as a treatment option for acute ischemic stroke in our department, most of the patients considered for this therapy could not receive thrombolytic therapy, mainly because of the time limit. Broad education of the public and referring physicians regarding the importance of early treatment may help to shorten these time intervals. Improvement in pre-hospital and in-hospital fast-track mechanisms may further improve the outcome. Intracranial hemorrhage is the major complication of thrombolytic treatment.

Chiu et al (10) prospectively investigated 30 patients in the Houston area treated with intravenous r-TPA. They concluded that r-TPA administration is feasible, safe, and efficacious when guidelines are carefully followed in an urban setting. In the ASSG report (11), 32 (35%) of 93 patients given r-TPA within 8 hours of stroke onset had evidence of blood on a computed tomogram (CT) done at 24 hours. Moreover, in the NIH trial, three symptomatic intracerebral hematomas (parenchymal hemorrhages) were documented clinically

and by CT (within 24 hours) in the 0- to 90-minute group (4%) and two in the 91- to 180-minute group (10%) (12). In our study there were no association between the duration of CVA to r-TPA administration and occurrence of ICH (neither symptomatic nor asymptomatic ICH).

ICH following r-TPA is due to reperfusion of cerebral vessels which their integrity has been disrupted by severe ischemia (13,14). Two publications have been reported on the risk factors of hemorrhagic transformation in patients who were treated with r-TPA after ischemic stroke, including NINDS (National Institute of Neurological Disorders and Stroke) and ECASS (European Cooperative Acute Stroke Study). (15, 16). Hemorrhagic transformations have been classified according to their appearance on CT in the ECASS, including hemorrhagic infarction (HI) and parenchymal hemorrhage (PH) (17,18). Also hemorrhagic transformations were classified into symptomatic or asymptomatic intracerebral hemorrhages in the NINDS r-TPA stroke trial. In contrast to the NINDS and ECASS (9,16), there were no significant association between NIHSS of patients at admission and the risk of hemorrhagic transformation in our study, this might be due to strict consideration of r-TPA protocol in our stroke center.

Risk factors for symptomatic intracerebral hemorrhage in the NINDS r-TPA stroke trial were the severity of neurological deficit at baseline, the presence of ischemic changes on pretreatment CT scan, and treatment with r-TPA (9).

High blood pressure, congestive heart failure and cardio-embolic stroke has been related to intracranial hemorrhage after r-TPA for ischemic stroke in both experimental and clinical settings (17-19). Larrue and colleagues reported that there were increased risk of hemorrhagic transformation in patients with cardio-embolic stroke, patients with congestive heart failure and patients with higher systolic blood pressure (20). In our study the symptomatic ICH was associated with the high systolic blood

pressure and atrial fibrillation with risk of hemorrhagic transformation (neither symptomatic nor asymptomatic ICH). It is probably due to limited number of patients in our study.

There is association between history of diabetes mellitus and serum glucose on admission and risk of symptomatic ICH. In long-standing diabetes, chronic microvascular damage may predispose vessels to rupture in the setting of ischemia (21). This factor may lead to increased hemorrhagic transformation (22).

In our study there was no significant association between history of diabetes mellitus and symptomatic ICH occurrence (neither symptomatic nor asymptomatic ICH). As Chiu et al described in their study, we also demonstrated that if the protocol is followed carefully, taking r-TPA is feasible and safe in our community.

Conclusion

In conclusion, thrombolysis in acute ischemic stroke in Iranian patients is safe and feasible provided that hospitals equipped with stroke unit and attached strictly to the guideline.

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References

1. Wardlaw JM, Zoppo G, Yamaguchi T, Berge E. Thrombolysis for acute ischaemic stroke. Cochrane database of systematic reviews (Online). 2003(3):CD000213. Epub 2003/08/15.
2. Hacke W, Donnan G, Fieschi C, Kaste M, von Kummer R, Broderick JP, et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet*. 2004;363(9411):768-74. Epub 2004/03/16.
3. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *The New England journal of medicine*.

2008;359(13):1317-29. Epub 2008/09/26.

4. Molina CA, Montaner J, Abilleira S, Arenillas JF, Ribo M, Huertas R, et al. Time course of tissue plasminogen activator-induced recanalization in acute cardioembolic stroke: a case-control study. *Stroke; a journal of cerebral circulation*. 2001;32(12):2821-7. Epub 2001/12/12.

5. Rha JH, Saver JL. The impact of recanalization on ischemic stroke outcome: a meta-analysis. *Stroke; a journal of cerebral circulation*. 2007;38(3):967-73. Epub 2007/02/03.

6. Ganz W. The thrombolysis in myocardial infarction (TIMI) trial. *The New England journal of medicine*. 1985;313(16):1018. Epub 1985/10/17.

7. 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(5):976-82. Epub 1992/05/01.

8. del Zoppo GJ, Pessin MS, Mori E, Hacke W. Thrombolytic intervention in acute thrombotic and embolic stroke. *Seminars in neurology*. 1991;11(4):368-84. Epub 1991/12/01.

9. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. The NINDS t-PA Stroke Study Group. *Stroke; a journal of cerebral circulation*. 1997;28(11):2109-18. Epub 1997/11/22.

10. Chiu D, Krieger D, Villar-Cordova C, Kasner SE, Morgenstern LB, Bratina PL, et al. Intravenous tissue plasminogen activator for acute ischemic stroke: feasibility, safety, and efficacy in the first year of clinical practice. *Stroke; a journal of cerebral circulation*. 1998;29(1):18-22. Epub 1998/01/28.

11. Wolpert SM, Bruckmann H, Greenlee R, Wechsler L, Pessin MS, del Zoppo GJ. Neuroradiologic evaluation of patients with acute stroke treated with recombinant tissue plasminogen activator. The rt-PA Acute Stroke Study Group. *AJNR American journal of neuroradiology*. 1993;14(1):3-13. Epub 1993/01/01.

12. 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; a journal of cerebral circulation*. 1992;23(5):632-40. Epub 1992/05/11.

13. Wang X, Tsuji K, Lee SR, Ning M, Furie KL, Buchan AM, et al. Mechanisms of hemorrhagic transformation after tissue plasminogen activator reperfusion therapy for ischemic stroke. *Stroke; a journal of cerebral circulation*. 2004;35(11 Suppl 1):2726-30. Epub 2004/10/02.

14. Maier CM, Hsieh L, Crandall T, Nara simhan

P, Chan PH. Evaluating therapeutic targets for reperfusion-related brain hemorrhage. *Annals of neurology*. 2006;59(6):929-38. Epub 2006/05/05.

15. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). *JAMA : the journal of the American Medical Association*. 1995;274(13):1017-25. Epub 1995/10/04.

16. Larrue V, von Kummer R, del Zoppo G, Bluhmki E. Hemorrhagic transformation in acute ischemic stroke. Potential contributing factors in the European Cooperative Acute Stroke Study. *Stroke; a journal of cerebral circulation*. 1997;28(5):957-60. Epub 1997/05/01.

17. Osseby GV, Benatru I, Sochurkova D, Urbinelli R, Megherbi SE, Couvreur G, et al. Trends in utilization of antithrombotic therapy in patients with atrial fibrillation before stroke onset in a community-based study, from 1985 through 1997. From scientific evidence to practice. *Preventive medicine*. 2004;38(2):121-8. Epub 2004/01/13.

18. Bowes MP, Zivin JA, Thomas GR, Thibodeaux H, Fagan SC. Acute hypertension, but not thrombolysis, increases the incidence and severity of hemorrhagic transformation following experimental stroke in rabbits. *Experimental neurology*. 1996;141(1):40-6. Epub 1996/09/01.

19. Levy DE, Brott TG, Haley EC, Jr., Marler JR, Sheppard GL, Barsan W, et al. Factors related to intracranial hematoma formation in patients receiving tissue-type plasminogen activator for acute ischemic stroke. *Stroke; a journal of cerebral circulation*. 1994;25(2):291-7. Epub 1994/02/01.

20. Larrue V, von Kummer RR, Muller A, Bluhmki E. Risk factors for severe hemorrhagic transformation in ischemic stroke patients treated with recombinant tissue plasminogen activator: a secondary analysis of the European-Australasian Acute Stroke Study (ECASS II). *Stroke; a journal of cerebral circulation*. 2001;32(2):438-41. Epub 2001/02/07.

21. Dietrich WD, Alonso O, Busto R. Moderate hyperglycemia worsens acute blood-brain barrier injury after forebrain ischemia in rats. *Stroke; a journal of cerebral circulation*. 1993;24(1):111-6. Epub 1993/01/01.

22. Kawai N, Keep RF, Betz AL. Hyperglycemia and the vascular effects of cerebral ischemia. *Stroke; a journal of cerebral circulation*. 1997;28(1):149-54. Epub 1997/01/01.