Comparison of MRI-based thrombolysis for patients with middle cerebral artery occlusion \leq 3 h and 3-6 h

Yue-Hua Li, Ming-Hua Li, Zhen-Guo Zhao¹, Qing-Ke Bai¹

Department of Radiology, The Sixth Affiliated People's Hospital, Shanghai Jiao Tong University, and ¹People's Hospital of Pudong New Area, Shanghai, China

Abstract

Objective: To investigate the outcomes of magnetic resonance imaging (MRI)based thrombolysis using recombinant tissue plasminogen activator (rt-PA) in patients with acute middle cerebral artery (MCA) occlusion in 3-6 hours. **Materials and Methods:** MRI-selected patients (n = 15) with acute ischemic stroke in MCA divided into two groups (\leq 3 h and 3-6 h) were treated with intravenous rt-PA. MR was performed before rt-PA, at 24 hours, 7 days, and 14 days after stroke. Recanalization was assessed 24 h after thrombolysis, and clinical status was evaluated before rt-PA treatment, 6 hours, 24 hours, 7 days, and 14 days after thrombolysis by the National Institutes of Health Stroke Scale (NIHSS). Modified rankin scale (MRS) was used to assess clinical outcome at 30 and 90 days after thrombolysis. **Results:** There was no significant between \leq 3 h and 3-6 h group in length of hospital stay, recanalization, MRS, and favorable outcome at 90 days. Recanalization within 24 hours occurred in 9 (60%), and nonrecanalization in 6 (40%). One patient in recanalization group and three in nonrecanalization group had an asymptomatic intracranial hemorrhage (ICH) within 24 h after thrombolysis (P = 0.235). Recanalization with thrombolysis was associated with a better outcome regardless of the time point of rt-PA treatment. Comparison with nonrecanalization group, recanalization was also associated with a lower NIHSS score at 14 days (P = 0.003), a lower TIMI grade at 7 days (P < 0.001), and a shorter length of hospital stay (P = 0.018). Conclusion: Our study suggested that MR-based thrombolysis using rt-PA was safe and reliable in patients with acute MCA occlusion in 3-6 hours.

Key words: Magnetic resonance imaging, middle cerebral artery, recombinant tissue plasminogen activator, stroke, thrombolysis

Introduction

Thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA), administered intravenously within 3 hours of onset, significantly improved neurological outcome in approximately 30% of patients with ischemic stroke.^[1] Although tPA is the only proven therapy for acute stroke, due to the narrow 3 hours therapeutic time window, the safety concerns of neurologists, internal medicine, and emergency physicians and other exclusion criteria,^[2,3] only 3% to 4% of all stroke patients are currently treated.^[4]

Patients with middle cerebral artery (MCA) occlusion have character including large infarct area, high new injury severity score (NISS) and so on. Whether thrombolysis treatment can be done for patients with MCA occlusion in 3-6 hours is a controversy. It is reported that MRI has

Address for correspondence: Dr. Yue-Hua Li, No. 600, Yi Shan Road, Shanghai - 200 233, China. E-mail: leeyuehuaxp@gmail.com

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been shown to be a useful tool for selection of patients for thrombolysis,^[5-8] especially reliable for assessment of recanalization in acute stroke, particularly in the setting of thrombolysis. In acute MCA occlusion, several studies suggest a recanalization rate of approximately 50% to 60% after thrombolysis with rt-PA.^[9-12] However, data on systematic assessment of rt-PA induced recanalization, with the MRI at different times after acute MCA stroke, are lacking. Therefore, the aim of the present study was to investigate the outcomes of MRI-based thrombolysis in acute MCA occlusion in 3-6 hours with respect to recanalization, clinical course, and cerebral bleeding complications.

Materials and Methods

Patients

Our study involved patients who had an acute ischemic stroke admitted within six hours after symptom onset. 135 consecutive patients were evaluated and underwent multiparametric MRI examinations between November 2005 and July 2008. A total of 46 patients with acute ischemic stroke of the anterior circulation and eligible for the following inclusion and exclusion criteria were promptly managed with IV rt-PA after MRI examinations, in which 15 patients who had acute stroke that involved the vascular territory of the MCA were included in this study. Seven patients were in 3 hours, and eight patients were in 3-6 hours after stroke onset. Data were prospectively obtained and entered into a local database, including information regarding age, sex, time of onset of symptoms, time of treatment, baseline National Institutes of Health stroke scale score (NIHSSS),^[13] before thrombolysis, at 6 and 24 hours, 7 and 14 days, modified rankin scale (MRS)^[14] score at 30 days and 90 days, the length of hospital stay, concomitant medication use, other relevant disease, MRI and CT data. All analyses were done retrospectively for the prospectively collected data set.

Patients were eligible for enrollment if they met the following criteria: (1) documented clinical signs and symptoms of acute MCA stroke lasting > 1 hour that were consistent with acute cerebral vascular infarction, including hemiparalysis, aphasia, and impaired levels of consciousness; (2) NIHSS scores ranging from 4 to 22; (3) age between 18-80 years; (4) thrombolytic therapy was administered within 6 hours of symptom onset; (5) nonICH confirmed by CT.

Patients were excluded if any of the following was present: (1) experienced intracranial hemorrhage (ICH), cerebral stroke of any etiology, or myocardial infarction in the past three months; (2) history of alimentary canal or urinary system hemorrhage, or trauma in last three weeks; (3) current anticoagulant therapy; (4) personal or family history of hemorrhagic tendency or hemorrhagic disease; (5) history of circulatory failure or uncontrolled hypertension (blood pressure, 180/100 mmHg), severe cardiac, renal, hepatic inadequacy, severe diabetes, or currently pregnancy. MR exclusion criteria: (1) Diffusion-weighted imaging (DWI) abnormality involving > 1/3 of MCA territory; (2) no perfusion deficit; (3) lacunar infarct; (4) emerge or remote hemorrhage. In addition, patients were also excluded if they lacked follow-up data for the following reasons: (1) MRI scanner was not available; (2) follow-up MRI or clinical scoring was refused; (3) MRI study was incomplete because of technical reasons or the subject's inability to cooperate; (4) patients with an apparent DWI lesion exceeded 70% of the territory of the ipsilateral hemisphere.

The study was approved by our institutional review board/ethics committee and was performed in accordance with declaration of Helsinki. All the enrolled patients gave their written informed consent.

Intravenous thrombolysis with rt-PA

10% of the total dosage (0.9 mg/kg) was injected as an intravenous bolus after one minute, while the rest was given by continuous intravenous infusion over the next 59 minutes-antiplatelet and neuroprotective agents would administer for the patients if no contraindications occurred 24 hours after thrombolysis.

MRI protocol

MRI was performed by GE 1.5 T dual gradient MR machine with parallel acquisition technique. MR examination includes spin echo-echo planar imaging weighted imaging (SE-EPI DWI), axial fast spin echo T2 weighted imaging (FSE T2WI), axial T1 fast spin echo weighted imaging (FSE T1WI), three-dimension-time of flight magnetic resonance angiography (3D TOF-MRA) and axial flow attenuated inversion recovery (FLAIR), perfusion weighted imaging (PWI). The examinations finished in ten minutes. Multiparametric protocol MRI was performed before the administration of rt-PA, 24 hours, 7 days and 14 days after thrombolysis, and the data were reviewed by two experienced neuroradiologists.

Pretreatment DWI lesion volumes were measured by the neuroradiologist of stroke center. The areas of hyperintensity on diffusion-weighted images were manually traced on each slice, summed, and multiplied with the slice thickness and inter-slice gap to obtain the DWI lesion volume.^[15] Recanalization was assessed from the follow-up MRI study on 6 hours on the basis of the PWI and MRA studies and classified according to the thrombolysis in cerebral infarction (TICI) classification^[16] and thrombolysis in myocardial infarction (TIMI) criteria^[17] [Grade 0, no recanalization/reperfusion; Grade 1, minimal recanalization/ reperfusion (<20%); Grade 2 incomplete recanalization/reperfusion; Grade 3, complete recanalization/reperfusion].

Follow-up protocol

The follow-up protocols included clinical and multiparametric protocol MRI follow-up, as well as head CT scan. Clinical follow-up conducted three months after thrombolysis included the changes of preliminary clinical presentation, the adverse events related to the thrombolysis, or the disease (defined as ischemic stroke, ICH, neurologic deficient, dead). Follow-up multiparametric protocol MRI was performed 24 hours, 7 days and 14 days after treatment. MRI assessment included the status of ischemic lesions, the changes of MRI parameters and recanalization of the occluded vessel. In all patients, a CT scan was repeated at 24 to 48 hours to evaluate the presence of ICH. Whenever a neurological worsening (NIHSS increase > 4 points) occurred, an additional CT scan was immediately performed to rule out symptomatic ICH. All MRI and CT were reviewed by a neuroradiologist who was blinded to clinical details.

Clinical assessment

We assessed clinical status before the administration of rt-PA and 6 hours, 24 hours, 48 hours, 7 days and 14 days after thrombolysis by means of the NIHSS,^[13] which was conducted by an experienced stroke neurologist. An ICH was defined as a CT-documented hemorrhage within 36 hours after thrombolysis and considered as symptomatic ICH, if the patient had clinical deterioration causing an increase of ≥ 4 points on the NIHSS and if the hemorrhage was likely to be the cause of neurological deterioration.^[1] MRS^[14] was used with a semistructured interview done either by telephone or in person to assess clinical outcome at 30 and 90 days after thrombolysis. All outcome variables (favorable outcome, independent outcome, hemorrhage, death) were assessed independently by physicians unaware of the patients' initial stroke severity, time to treatment, and imaging modality applied. Favorable outcome at day 90 was defined as a MRS score of 0-2.

Statistical analysis

All statistical analyses were performed using the SPSS package, version 13.0 (SPSS, Chicago, Illinois, US). Data are presented as the mean \pm standard deviation. Statistical significance for intergroup differences was assessed by the two-tailed Fisher's Exact Test and χ^2 -test for categorical variables and by the Kruskal-Wallis and Mann-Whitney *U* test for continuous variables. A two sided *P* value of \leq 0.05 was considered to indicate statistical significance.

Results

The characteristics of MRI-selected rt-PA patients with acute stroke in MCA are summarized in Table 1. Table 1 shows the characteristics of time to treatment groups ($\leq 3 \text{ h} vs. 3\text{-}6 \text{ h}$). In this subgroup, no variables were found significantly difference between the two groups. The time from symptom onset to the initial MRI study was 140.43 \pm 39.23 mins in $\leq 3 \text{ h}$ group and 273.25 \pm 58.73 mins in 3-6 h group. The NIHSS score was 13.14 \pm 2.85 and 13.86 \pm 4.79 at baseline. The corresponding initial DWI lesions volume was 55.71 \pm 18.15 and 60.38 \pm 36.60. The mortality and the symptomatic ICH from this study was zero. Four patients had an asymptomatic ICH in 24 h after thrombolysis. Recanalization within 24 hours occurred in 9 (60%, Figures 1 and 2), and nonrecanalization in 6 (40%).

Table 2 shows the characteristics of the recanalization (n = 9) and nonrecanalization (n = 6) group. In this group, there were no significant differences in NIHSS score at the baseline and 6 h after thrombolysis (P > 0.05), whereas the NIHSS score at 24 h, 7 days, and 14 days after treatment in recanalization group were significantly lower than those in nonrecanalization group (P = 0.050, P = 0.012, and P = 0.003). The MRS score at 90 days in recanalization group was

Table 1: Baseline and outcome characteristics of patients treated with tPA within <3 hours and 3 to 6 hours					
	Time to	Time to	Р		
	treatment	treatment	value		
	(≤3 h)	(3-6 h)			
	(n = 7)	(n = 8)			
Age (years)	61.57 ± 10.84	65.75 ± 7.63	0.536		
(mean ± SD)					
Female/male	3/4	2/6	0.608		
Time to	140.43 ± 39.23	273.25 ± 58.73	< 0.001		
thrombolysis (min)					
Infarction of left side,	4 (66.7)	6 (66.7)	0.608		
n (%)					
NIHSSS at baseline	13.14 ± 2.85	13.86 ± 4.79	0.694		
6 h	9.86 ± 1.95	13.00 ± 7.03	0.336		
24 h	8.71 ± 3.09	10.36 ± 6.55	0.779		
7 days	6.29 ± 3.04	18.13 ± 5.38	0.694		
14 days	4.29 ± 2.63	6.00 ± 3.33	0.281		
MRI lesion volume	55.71 ± 18.15	60.38 ± 36.60	0.867		
(in ml)					
Length of hospital	11.71 ± 4.75	17.75 ± 11.66	0.397		
stay (days)					
Recanalization, n (%)	5 (55.56)	2 (33.3)	0.550		
asymptomatic ICH	1	3	0.569		
MRS at 90 days	1.86 ± 0.89	2.13 ± 1.46	0.613		
Favorable outcome	4	3	0.608		
at 90 days					
TIMI before	0.00 ± 0.00	0.38 ± 0.52	0.232		
thrombolysis					
TIMI at 24 h	2.00 ± 1.41	1.50 ± 1.41	0.536		
TIMI at 7 days	2.00 ± 1.41	1.63 ± 1.30	0.613		

ICH - Intracranial hemorrhage; TIMI - Thrombolysis in myocardial infarction



Figure 1: MRI images in a 70-year-old man with a sudden coma of 100 minutes and a NISS score of 18 before thrombolysis; (a-c) MRI shows a large area of hyperintense on DWI with no abnormity on T1WI before thrombolysis, and 3D-TOF MRA exhibits occlusion of the left MCA; (d-f) MRI confirms hyperintense on DWI and T2WI with recanalization of the left MCA on 3D-TOF 24 hours after thrombolysis; (g-i) MRI displays diminution of the lesion on T2WI with recanalization of the left MCA on 3D-TOF 24 hours after thrombolysis; (g-i) MRI displays diminution of the lesion on recanalization of the left MCA on 3D-TOF 14 days after thrombolysis

significantly lower than that in nonrecanalization group (P < 0.001). Favorable outcome at 90 days was reported for 55.56% of patients in recanalization group and 0% in nonrecanalization group (P = 0.044), and independent outcome was achieved in 44.44% patients in group A, and 16.67% in group B (P = 0.580), so allowing safe and effective thrombolytic treatment (MRS score ≤ 2) in 100% of the patients in group A and 16.67% in group B (P = 0.002). There was no significant difference in the average TIMI grade before

thrombolysis, but the average TIMI grade at 24 h and 7 days after thrombolysis in recanalization group were significant lower than those in nonrecanalization group (P < 0.001). In addition, recanalization following thrombolysis was strong predictors for a good outcome, less asymptomatic ICH, and short hospital stay [Table 2]. There were no significantly differences in age, gender, time to treatment, involved hemisphere, DWI infarction volume between the two groups.



Figure 2: MRI images in a 67-year-old woman with a sudden coma of 220 minutes and a NISS score of 15 before thrombolysis; (a-c) MRI shows a large area of hyperintense on DWI with no abnormity on T1WI before thrombolysis, and 3D-TOF MRA exhibits occlusion of the right MCA; (d-f) MRI confirms hyperintense on DWI and T2WI with some degree of recanalization of the right MCA on 3D-TOF 24 hours after thrombolysis; (g-i) MRI displays the lesion on T2WI with recanalization of the right MCA on 3D-TOF seven days after thrombolysis; (j-l) MRI demonstrates diminution of the lesion on T2WI with recanalization of the right MCA on 3D-TOF 14 days after thrombolysis

Discussion

The major findings of the present study are as following: (1) there were no significant difference between ≤ 3 h group and 3-6 h group; (2) a 60% rate of MCA recanalization following thrombolysis with rt-PA was seen in this study; (3) patients with recanalization were associated with improved clinical scores, good outcome, less asymptomatic ICH and shorter hospital stay; (4) no

symptomatic cerebral bleeding and mortality occurred in this study.

In acute MCA occlusion, the true recanalization rate of intravenous rt-PA in ischemic stroke is not known presently, but several case-control studies suggest a recanalization rate of approximately 50% to 60% after full dosage rt-PA treatment.^[5,6,9,10] Recently, Tran cranial Doppler sonography studies revealed surprisingly high recanalization rates, up to 70%,

	Recanalization	Nonrecanalization	Р
	(n = 9)	(n = 6)	value
Age (years)	64.33 ± 8.22	63.00 ± 11.24	0.776
(mean ± SD)			
Female/male	4/5	1/5	0.580
Time to thrombolysis (min)	192.22 ± 76.65	239.83 ± 193.89	0.328
Infarction of left side, n (%)	6 (66.7)	4 (66.7)	0.999
NIHSSS at baseline	13.22 ± 3.77	14.00 ± 4.38	0.776
6 h	10.11 ± 5.18	12.67 ± 4.13	0.224
24 h	7.56 ± 4.85	12.67 ± 4.13	0.050
7 days	4.89 ± 2.93	10.83 ± 3.87	0.012
14 days	3.33 ± 1.87	8.00 ± 2.19	0.003
MRI lesion	54.33 ± 25.18	64.00 ± 34.72	0.689
volume (ml)			
Length of hospital	10.67 ± 6.12	21.33 ± 10.13	0.018
stay (days)			
Stroke time	5 (55.56)	2 (33.3)	0.608
≤3 hours, n (%)			
Asymptomatic ICH	1	3	0.235
MRS at 90 days	1.22 ± 0.83	3.17 ± 0.41	< 0.001
Favorable outcome	5 (55.56%)	0	0.044
at 90 days			
Independent	4 (44.44%)	1 (16.70%)	0.580
outcome			
at 90 days			
TIMI before	0.22 ± 0.44	0.17 ± 0.41	0.864
thrombolysis			
TIMI at 24 h	2.18 ± 0.44	0.17 ± 0.41	< 0.001
TIMI at 7 days	2.78 ± 0.44	0.33 ± 0.52	< 0.001

Table 2: Baseline and outcome characteristics of patients
treated with r-tPA with recanalization and nonrecanalizatior

Note: ICH = Intracranial hemorrhage; TIMI = Thrombolysis in myocardial infarction

with intravenous rt-PA within the first six hours.^[19-21] The 60% rate of recanalization after intravenous thrombolysis was seen in this study and was in line with those from previous studies.^[5,6,9,10] Although our group of patient was too small to give a reliable estimate of the true recanalization rate in MCA occlusion after intravenous thrombolysis, the level of significance decreased for all outcome scales in intergroup comparisons demonstrated a significant benefit of recanalization.

Recanalization following intravenous rt-PA within < 6 hours of stroke onset led to neurological improvement, and better clinical outcome, than was seen in nonrecanalization subjects.^[9] We actually reproduced these findings in our sample. Recanalization with thrombolysis was associated with a better outcome regardless of the time point of rt-PA treatment (\leq 3 hours or 3 to 6 hours) (univariate analysis: MRS \leq 2, P = 0.002; MRS \leq 1, P = 0.044) and a lower NIHSS score at 14 days (P = 0.003). In addition, recanalization was also associated with a lower TIMI grade at 7 days (P < 0.001), and a shorter length of hospital stay (P = 0.018).

The reason for therapeutic effect of rt-PA is recanalization of the occluded artery. Although, the intravenous rtPA

trials, including ECASS I and II, NINDS, and alteplase thrombolysis for acute noninterventional therapy in ischemic stroke (ATLANTIS),^[1,22-24] did not assess whether clinical improvement depended on initial vessel occlusion with subsequent recanalization after thrombolytic therapy or on the rate of spontaneous vessel reopening, our study and other series^[5,6,9,11] demonstrated that recanalization following thrombolysis resulted in a better outcome than that in nonrecanalization group. In this study, all selected patients with acute stroke in MCA occlusion within 6 h were prompted for thrombolysis with rt-PA after MRI examination without delay, the average MRS at 90 days was 2.0 ± 1.20 $(1.22 \pm 0.83$ in recanalization group and 3.17 ± 0.41 in nonrecanalization group), but no symptomatic cerebral bleeding and mortality occurred. Therefore, our data suggested that an aggressive means of thrombolysis should be administered for these patients with MCA occlusion who were suitable for MR criteria even if no recanalization was observed, because a persisting vessel occlusion is associated with large infarcts and an unfavorable clinical outcome. On occasions, a good collateral flow may result in a good clinical outcome, despite persisting MCA occlusion. Our findings strengthen the hypothesis that early thrombolysis of an obliterating thrombus by rt-PA with subsequent recanalization of a major cerebral artery is the basis for an improved clinical outcome in many patients.

Molina and colleagues^[9] have confirmed that patients treated within the 3 h time window showed higher recanalization rates than the 3 to 6-hour group (TIMI recanalization had an effect on the MRS: 67.6% patients with TIMI 2 to 3 had a good outcome). However, within a homogeneous sample of MRI-selected patients treated by IV rt-PA in our study, we found no difference in NIHSSS at baseline and after thrombolysis, MRI lesion volume, recanalization rates, asymptomatic ICH, TIMI before and after thrombolysis, and clinical outcomes parameters between patients within 3 h and 3-6 h. In other words, the time point of rt-PA therapy did not affect the recanalization rate (P = 0.550), symptomatic ICH (P = 0.569), and clinical outcomes parameter (P = 0.608). The main reason for this difference between our study and Molina and colleagues^[9] was that the sample was too small to give a reliable estimate of the true recanalization rate after intravenous thrombolysis. Moreover, the selection of patients with the use of multi-parametric protocol MRI was likely to account for some of the difference. There is no doubt that patients with a confirmed relevant amount of tissue at risk of infarction will be more likely to benefit from reperfusion therapy.

The major complication of IV rt-PA therapy is ICH.^[18,25] However, there was no symptom ICH in this study, and only four patients had an asymptomatic ICH with 24 h after thrombolysis. The symptomatic ICHs are clinically catastrophic and neurological deterioration. In contrast, asymptomatic ICHs are not clinically catastrophic and have no symptoms. The incidence of asymptomatic hemorrhage after intravenous thrombolysis was found to be 9.9 % from combined CT-based data of the NINDS rt-PA trial^[1] and the ATLANTIS trial.^[23,24] In this study, the 26.7 % rate of asymptomatic ICH were higher than that of the previous reports (9.9 %),^[1,23,24] but none of the patients developed symptomatic ICHs due to no symptoms and NIHSS score deterioration. The first reason for none symptomatic hemorrhage in this study may attribute to strict clinical and multi-parametric protocol MR criteria for patient selection. Patients with signs of severe stroke, intracerebral hemorrhage, and large DWI lesions were excluded from thrombolysis.

As compared with the previous randomized or nonrandomized MRI-based rt-PA treatment trials, our study has several differences: No mortality and symptomatic ICH. Multiparametric protocol MRI, including T1WI, T2WI, DWI, PWI, 3D TOF-MRA, and FLAIR, was completed in ten minutes. So the slogan of time is brain has been anchored deep inside the mind of every neurologist and neuro-radiologist treating patients with acute stroke.

Several methodological limitations of the presented study should be mentioned. The first one is the relatively small number of patients examined. This was a result of the generally low number of patients fulfilling the strict time criteria for thrombolytic therapy, event with MCA occlusion. Secondly, quantification of infarct volume was performed manually, because no semiautomatic quantification software was available. Therefore the quantification could have been affected by subjective operator error. Thirdly, this was a prospective study with nonrandomized, noncontrolled trial. In addition, late assessment of recanalization after 24 hours prevents us from differentiating between persistent occlusion and early re-occlusion after initial recanalization.

In this study, our data suggested that MRI-based thrombolysis with rt-PA was safe and reliable in selected patients with acute MCA stroke within 3-6 h. Further controlled and randomized studies are needed to establish the efficacy of thrombolysis with the MRI-based multiparametric protocol.

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