

Original Article

Therapeutic effect of recombinant tissue plasminogen activator on acute cerebral infarction at different times

Ming Liu, Hai-rong Wang, Jia-fu Liu, Hao-jun Li, Shen-xing Chen, Sha Shen, Shu-ming Pan

Department of Emergency Medicine, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai 200092, China

Corresponding Author: Shu-ming Pan, Email: drshumingpan@gmail.com

BACKGROUND: The study aimed to compare the therapeutic effect of recombinant tissue plasminogen activator (rt-PA) on the onset of acute cerebral infarction (ACI) at different time points of the first 6 hours.

METHODS: A retrospective analysis was conducted in 74 patients who received rt-PA thrombolysis treatment within 4.5 hours after ACI and another 15 patients who received rt-PA thrombolysis treatment between 4.5–6 hours after ACI.

RESULTS: National Institute of Health Stroke Scale (NIHSS) scores were statistically decreased in both groups ($P>0.05$) at 24 hours and 7 days after ACI. There was no significant difference in modified ranking scores and mortality at 90 days after the treatment between the two groups ($P>0.05$).

CONCLUSIONS: The therapeutic effect and mortality of rt-PA treatment in patients with ACI between 4.5–6 hours after the onset of the disease were similar to those in patients who received rt-PA within 4.5 hours after the onset of this disease. Therefore, intravenous thrombolytic therapy for ACI within 4.5–6 hours after ACI was effective and safe.

KEY WORDS: Acute cerebral infarction; Thrombolysis; Recombinant tissue type plasminogen activator

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INTRODUCTION

Cerebral stroke ranks second among the diseases which cause death in China, and is the leading cause of disability worldwide.^[1-4] About 6–7 million people suffered from this disease, with the appearance of around 2 million new cases every year. And approximately 1.5 million patients die each year. It tops among the diseases which cause disabilities, and patients with acute cerebral infarction (ACI) accounted for 60%–80% of all the cerebral stroke patients. ACI is characterized with a high disability rate and a high mortality rate. Currently, recombinant tissue type plasminogen activator (rt-PA) is one of the most effective methods in the treatment of ACI within the limited 4.5-hour timeframe.^[5] For patients with ACI, time is very crucial. As a thrombolysis drug,

rt-PA is considered as the first choice only if patient's conditions permit. The sooner the treatment begins, the better the efficacy would be.^[6,7] Our department has a multidisciplinary team in collaboration with the departments of neurology, neurosurgery, radiology, and clinical laboratory in the second half of year 2008. In this study, cerebral stroke patients were primarily selected from the department of emergency medicine to enter the green channel. Inquiry on medical history and the National Institute of Health Stroke Scale (NIHSS) evaluation should be completed within 10 minutes, and head CT and relevant blood analysis within 45 minutes. The medical condition of the patient was evaluated by the stroke team. rt-PA thrombolysis for ACI was performed in the stroke unit of green channel after

informed consent form was signed by family members of the patient. However, some patients failed to be sent to hospital immediately after the disease occurred for various reasons such as lack of awareness of the disease. For those patients who were within 4.5–6 hours after ACI, a selectively emergency thrombolysis treatment would be performed after thorough evaluation based on their conditions, relevant risk factors, and requirements of their families. This study aimed to summarize the effect of rt-PA thrombolysis treatment in ACI patients within 4.5 hours and between 4.5–6 hours after the occurrence of the disease.

METHODS

Inclusion criteria

Immediate ascertainment of stroke cases was based on clinical presentation and findings on computed tomography (CT) of the brain according to the guidelines.^[8] The following diagnosis of cerebral infarction was made in accordance with the standards for diagnosis of cerebral infarction formulated at the Fourth National Congress on Cerebrovascular Disease in 1995 and with the National Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke 2010.^[9] The standards or guidelines included: (1) age, 18 – 80 years old; (2) time point, within 6 hours after ACI; (3) physical signs of brain function damage persisted for 1 hour, and paralysis <degree 3; (4) intracranial hemorrhage excluded by cerebral CT, and no images indicating massive cerebral infarction; (5) informed consent form signed by the patient or his/her family.

Exclusion criteria

According to the National Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke 2010, the following patients were excluded:^[9] 1) patients with intracranial hemorrhage including suspicious hemorrhage in the subarachnoid space, trauma in the head in recent 3 months, gastrointestinal hemorrhage or urinary system hemorrhage in recent 3 weeks, major surgery in recent 2 weeks, arterial puncture sites where hemostasis by compression is not convenient to perform in recent 1 week; 2) patients with cerebral infarction or myocardial infarction in recent 3 months, excluding old lacunula infarction without sequelae of neurological symptoms; 3) patients with severe cardiac, hepatic or renal diseases or those with diabetes mellitus; 4) patients with signs of active hemorrhage or trauma (such as fracture) shown by physical examination; 5) patients taking oral anti-

coagulation drugs, and International Normalized Ratio (INR) >15; patients subjected to heparin therapy within 48 hours (APrT exceeding normal range); 6) patients with platelet count below $100 \times 10^9/L$, blood glucose <2.7 mmol/L; 7) patients with blood pressure >180 mmHg or diastolic pressure >100 mmHg; 8) patients in the period of gestation; 9) patients who are not coordinative.

General information

Eighty-nine ACI patients received rt-PA thrombolysis treatment in our department between June 2010 and June 2012. Among them, 74 patients had thrombolysis treatment within 4.5 hours (group A), and 15 had the same treatment within 4.5–6 hours after onset of the disease (group B).

The average age of patients in groups A and B was 63.7 ± 9.2 , 64.3 ± 9.1 , respectively ($P > 0.05$). There were no statistical differences in gender and ACI risk factors between the two groups, such as rates of patients with hypertension, diabetes mellitus, and atrial fibrillation ($P > 0.05$).

Treatment method

rt-PA 0.9 mg/kg (maximal dosage 50 mg) was administered. At first, 10% was intravenously injected within 1 minute, and the rest 90% was continuously infused by an intravenous pump within 60 minutes. Thrombolysis treatment was stopped if severe headache, rapid elevation of blood pressure, nausea or vomiting reoccurred. Head CT was used in case of cerebral hemorrhage. Anti-coagulation agents including aspirin were not administered within 24 hours after thrombolysis treatment. Platelet and blood coagulation function were re-examined immediately if cerebral hemorrhage appeared, and fresh plasma or 1U platelet was transfused. Four items of blood coagulation and head CT were examined 24 hours after thrombolysis treatment. Low molecular weight heparin was subcutaneously injected for 7 days, and changed to oral administration. Treatments that can improve brain cell metabolism were also administered at the same time.

Efficacy evaluation

US NIHSS was adopted before, 24 hours, and 7 days after thrombolysis treatment. Modified Rankin Scale was used to evaluate patients' abilities of daily life 90 days after thrombolysis treatment.^[10]

Statistical analysis

Measurement data were expressed as mean \pm standard

deviation. Student's *t* test was used for comparison of scores before the treatment; and the Chi-square test was used for comparison of the measurement data. SAS 6.12 statistical software was used for statistical analysis. $P < 0.05$ was considered statistically significant.

RESULTS

Comparison of NIHSS scores between the two groups

The patient mortality rate was 6.8% in group A, and 6.7% in group B ($P > 0.05$). All the patients died from cerebral hemorrhage. Therefore, the deaths could be excluded from statistical analysis of therapeutic effect.

The onset NIHSS scores in group B (6.50 ± 1.61) was significantly lower than that in group A (9.46 ± 4.95) ($P < 0.01$). After thrombolysis treatment, NIHSS scores decreased in groups A and B. NIHSS scores in group A decreased to 3.55 ± 5.20 at 7 days after thrombolysis treatment ($P < 0.01$) (Figure 1). For the patients in group B, NIHSS scores decreased to 2.43 ± 2.82 at 24 hours after thrombolysis treatment ($P < 0.01$), and to 1.57 ± 2.28 at 7 days ($P < 0.01$) (Figure 1). The results indicated that rt-PA thrombolysis treatment was useful for the patients.

There was no statistical difference in decrease of NIHSS scores at 24 hours and 7 days after thrombolysis treatment. NIHSS scores in group A at 24 hours after thrombolysis treatment decreased by 5.10 ± 4.03 and in group B by 4.07 ± 3.15 ($P > 0.05$); at 7 days, NIHSS scores in groups A and B decreased by 5.91 ± 4.43 , 4.93 ± 2.67 ($P > 0.05$) (Figure 2).

Comparison of abilities of daily lives between the two groups

Using modified Rankin scale, we followed up the ACI patients for their comprehensive abilities of daily lives at 90 days after thrombolysis treatment. Rankin score was 1.72 ± 1.73 for the patients in group A and 1.14 ± 1.35 for the patients in group B, and there was no significant difference ($P > 0.05$). The results indicated that the comprehensive abilities of daily lives for patients in the two groups were similar (Figure 3).

Adverse reactions and complications

In group A, cerebral hemorrhage occurred in 8 patients, with an incidence of 11.6%. Among the 8 patients, 5 died, 1 had gum bleeding, and 1 was complicated with gastrointestinal hemorrhage. In group B, 2 patients had cerebral hemorrhage, with an incidence of 18.2%. Only one patient died. There was no significant

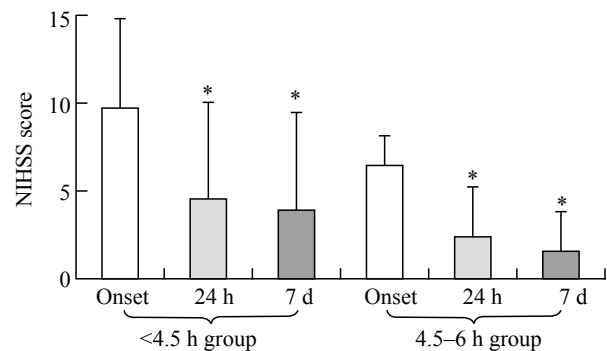


Figure 1. Comparison of NIHSS scores between the two groups before and after thrombolysis. Compared within the same group, $*P < 0.05$.

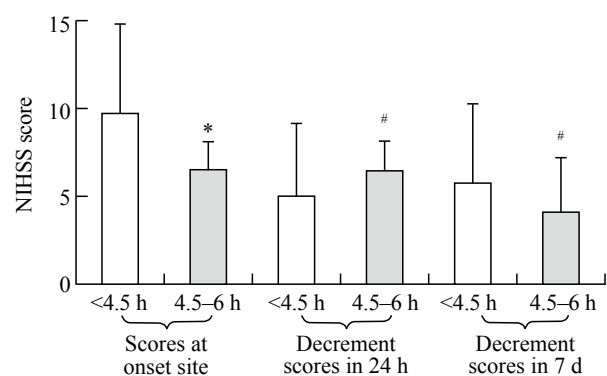


Figure 2. Comparison of decrease of NIHSS scores of patients after thrombolysis between the two groups. $*P < 0.05$, $\#P > 0.05$.

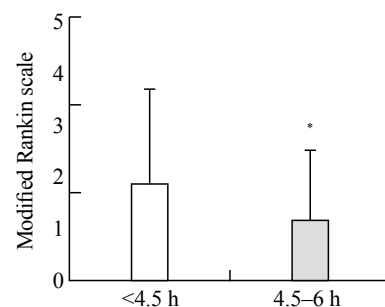


Figure 3. Modified Rankin scores of patients in the two groups 90 days after thrombolysis. $*P > 0.05$.

difference between incidences of cerebral hemorrhage in the two groups ($P > 0.05$).

DISCUSSION

ACI has a high mortality and a disability rate. Emergency rt-PA thrombolysis treatment has become one of the best therapeutic treatments since it was first reported by a research team of NIHSS in 1995. It was reported that recombinant tissue plasminogen activator (rt-PA) could significantly improve the clinical symptoms of patients with acute cerebral infarction at a

super early stage within 3 hours, and could significantly reduce the rate of disability.^[11] Intravenous rtPA is the only approved medical therapy for ACI in China.^[2] Extending the rtPA treatment window is an important strategy for maximizing thrombolytic therapy in patients with ACI. The European Cooperative Acute Stroke Study (ECASS) III in 2008 extended the time points for rt-PA thrombolysis for ACI from 3 hours to 4.5 hours, although with a higher symptomatic intracranial hemorrhage (SICH) rate, but no change in mortality.^[12] The result has been well acknowledged in academic circles.^[2, 13-16] In general, the earlier thrombolysis treatment begins, the better the effect would be and the less risk there is.^[1] At present, rt-PA thrombolysis treatment given within 4.5 hours after occurrence of the disease is safe and effective, but few studies have focused on the effects of rt-PA thrombolysis performed within 4.5–6 hours after occurrence of the disease.

ACI consists of a central necrosis area and a surrounding ischemic penumbra area. Brain cells die in the necrosis area because of total ischemia. Collateral circulation in the surrounding ischemic penumbra area provides partial blood supply. Therefore, there are a lot of viable nerve cells in this area. Gradually, the central necrosis area expands and the penumbra area shrinks. With an aggravation of ischemia and prolonged ischemic time, only few nerve cells can survive. Nerve cells in the ischemic penumbra area recover their functions if cerebral metabolism could be rapidly improved by blood supply.^[17] Therefore, the earlier thrombolysis treatment for ACI patients is performed, the better effective will be. Researches indicate that the penumbra area is found in around 70% of patients who had examination within 6 hours after stroke. This means that it is possible to expand the time of thrombolysis treatment up to 6 hours.^[18] Based on the reported studies, we performed rt-PA thrombolysis on patients within 4.5–6 hours after the occurrence of the disease in order to explore the efficacy of thrombolysis within this period.

The present study revealed that NIHSS scores of patients in both groups decreased significantly after thrombolysis treatment. Obviously, rt-PA was effective in reducing neurologic impairment, improving patients' prognosis and strengthening patients' ability to live independently. Since there was no statistical difference in decrease of NIHSS scores at 24 hours and 7 days after thrombolysis treatment between the two groups, the short-term effects were similar. There was also no statistical difference in modified Rankin scores at 90 days, and the ability of daily lives of the patients was almost the same

between the two groups. The patients only had mild sequelae, and were basically able to live independently. The death rate in the two groups was approximately 6.7%, which was lower than the results of the NINDS test (17%) and ECASS test (22.4%).^[6,11] Therefore, we consider that it is safe to perform rt-PA thrombolysis within 4.5–6 hours after the onset of ACI. García-Bermejo et al^[19] has the same result. In our study, however, the patients who received rt-PA thrombolysis within 4.5–6 hours after the onset of ACI had relatively lower NIHSS scores. We recommend that in those hospitals with experiences in rt-PA thrombolysis treatment, the time of thrombolysis can be extended up to 6 hours in ACI patients with lower NIHSS scores if their conditions are evaluated.

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Ethical approval: The study was approved by the Medical Ethics Committee of Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China.

Conflicts of interest: The authors declare that there is no conflict of interest.

Contributors: Liu M and Wang HR contributed equally to this study. Liu M proposed the study, analyzed the data and wrote the first drafts. All authors contributed to the design and interpretation of the study and to further drafts.

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