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Original Article

# Intravenous Thrombolytic Therapy Using Low-Dose rt-PA in a Broadened Therapeutic Window for Ischemic Stroke Treatment Under Multimode Magnetic Resonance Imaging Monitoring

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SUMMARY

*Background:* To evaluate the efficacy and safety of intravenous thrombolytic therapy (TT) using low-dose rt-PA in a broadened therapeutic window (TW) for ischemic stroke treatment under multimode magnetic resonance imaging (MRI) monitoring.
*Methods:* A total of 45 patients with ischemic stroke occurring within 4.5–6 h prior to treatment were divided into two groups: thrombolytic group (Group A) and non-thrombolytic group (Group B). Another set of 25 patients with ischemic stroke occurring within 4.5 h were classified into Group C. Low-dose rt-PA was administered in Group A, standard-dose rt-PA in Group C, and normal therapy in Group B. All the patients were evaluated using the National Institutes of Health Stroke Scale (NIHSS) scores before and 24 h after treatment and modified Rankin scale (mRS) scores 90 days after treatment.
*Results:* The post-treatment NIHSS score and day-90 mRS score in Groups A and C were significantly different from those in Group B ($p < 0.05$).
*Conclusion:* Intravenous TT using low-dose rt-PA in a broadened TW for ischemic stroke treatment under multimode MRI monitoring is safe and effective.



## 1. Introduction

Evidence-based medical studies showed that intravenous thrombolytic therapy (TT) using low-dose rt-PA for acute ischemic stroke (AIS) within the therapeutic window (TW) was safe and efficient; it can dredge blocked vessels and restore the blood supply and consequently save the ischemic penumbra (IP).[1–4] However, the TW was strictly limited to 3 h, and some researchers indicated that TT in a broadened TW might increase the occurrence of fatal intracerebral hemorrhage (ICH).[5,6] According to statistics, only less than 5% of the patients with AIS received TT on time, as the others had exceeded the TW.[7] Although the European Cooperative Acute Stroke Study III in 2008 proved that the TW could be extended to 4.5 h,[8] many patients were still excluded from TT. Additional similar studies were then performed; though the results of these studies were different, a similar doubt on the safety of extending the TW was noted.[9,10] Recent studies on the pathophysiological mechanism of AIS and magnetic resonance imaging (MRI) findings of the IP indicate that the only goal of TT is saving the IP,[11] and the therapy becomes useless if the IP does not exist.[12] Clinically, the IP is evaluated using magnetic resonance perfusion-weighted imaging (PWI) and diffusion-weighted imaging (DWI).[13] Based on the imaging results, the IP can still be observed in some patients with AIS using a broadened TW, indicating a potential positive prognosis in performing TT. We screened patients with AIS 4.5–6 h from the onset of the stroke to the time of evaluating the IP using multimode MRI. Perfusion-diffusion mismatch (PDM) was defined when the perfusion lesion area was 20% larger than the diffusion lesion area.[14,15] Low-dose rt-PA[16] was administered to mismatch patients during TT to reduce the incidence of complications, such as lethal ICH. Our study primarily focused on monitoring the efficacy and safety of intravenous TT using low-dose rt-PA in a broadened TW and provided evidence for further treatment.

## 2. Materials and methods

### 2.1. Subjects

In this prospective study, 45 patients with AIS admitted to the Department of Neurology of our hospital between January to October 2016 within 4.5–6 h from stroke onset were selected. All patients underwent MRI (GE3.0T) before thrombolysis based on the $T_1$WI, $T_2$WI, FLAIR, DWI, PWI, and MRA (DWI: TR/TE = 10,000/106.5 ms; matrix, 128 × 128; visual window, 24 × 24 cm; b = 1000; PWI: TR/TE = 2000/80 ms; visual window, 24 × 24 cm; turning angle, 90°; layer, 6 mm; interval, 1.5 mm; matrix, 128 × 128, scanned for 11 layers with 30 phases continually to obtain 330 images). When the first original images appeared on the monitor, 15 mL of dimeglumine gadopentetic acid was injected at the rate of 2 mL/s using a high-pressure syringe. Thereafter, 15 mL of saline was injected to wash the pipe. The entire scanning process lasted for approximately 15 min. The images were analyzed using GE Advantage Windows work-

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station Functool 2 and double checked by two experienced radiologists. Mismatch was defined as more than 20% perfusion image error son PWI and DWI. The patients were divided into two groups according to their PDM results: Group A included 20 mismatch patients, to whom low-dose rt-PA was administered; Group B included 25 match patients, to whom strengthening antiplatelet therapy was provided. Another 25 patients with stroke occurring less than 4.5 hprior to treatment were included and classified into Group C and received the same therapy as Group A. All the patients met the AIS criterion revised in the 4$^{th}$ Congress of Cerebrovascular Disease, Chinese Medical Association. Those in Group C met the indications mentioned in the 2010 Chinese AIS Intravenous Thrombolytic Therapy Guideline. The criteria for Groups A and C were similar, except for the TW, which was extended to 6 h in the former group. Routine examinations, including electrocardiography, blood routine examination, coagulation tests (four items), and blood sugar level determination, were performed in all patients before treatment. All the patients' conditions were graded using the National Institutes of Health Stroke Scale (NIHSS) before TT. The patients fit the indication to have mechanical thrombectomy and NIHSS score of $\geq 12$ would be excluded, since they need intravascular stent embolectomy. No significant differences in the general information were observed among the three groups (Table 1).

The NIHSS score was assessed in all patients before treatment and 24 h and 7 days after treatment and the modified Rankin scale (mRS) score 90 days after treatment to evaluate neurological deficits. Craniocerebral MRI, DWI, and susceptibility-weighted imaging (SWI) were performed in all the patients from 24–48 h after treatment to assess the efficacy of TT and monitor the occurrence of ICH. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Linyi People's Hospital Brain Hospital. Written informed consent was obtained from all participants.

### 2.2. Patient treatment

Low-dose rt-PA (Boehringer Ingelheim, Germany) was administered to all the patients in Groups A and C for intravenous TT, with a door-to-needle time of approximately 60 min. The loading dose (injected at < 1 minute) of rt-PA in Group A was 10% of the standard dose, which was calculated as follows: 10% × 0.9 mg/kg × weight; the total dose was of the low dose, and the remaining dose was pumped for 1 hour. The low dose was defined as a total amount of 50 mg for normal-weight patients (50 mg was much safer and had the same effectiveness) and 70 mg for patients with obesity ($\geq$ 90 kg); the final dose was 0.6 to 0.8 mg/kg. In Group C, the standard dose was used; the loading dose (injected at < 1 minute) was also 10% of the standard dose calculated as follows: 10% × 0.9 mg/kg × weight, while the remaining total standard dose was pumped within an hour. Head computed tomography or MRI + SWI was performed in the patients 1 day after treatment to exclude ICH. Thereafter, 100 mg/day of aspirin and 75 mg/day of clopidogrel (oral), together with other routine treatments, were administered to the patients in all three groups.

**Table 1**
General information.

| Items | A (n = 20) | B (n = 25) | C (n = 25) | p |
|---|---|---|---|---|
| Male (n, %) | 15 (75) | 17 (68) | 18 (72) | > 0.05 |
| Age | 62.2 ± 5.9 | 65.2 ± 4.6 | 64.1 ± 6.7 | > 0.05 |
| Hypertension | 12 | 16 | 17 | > 0.05 |
| Diabetes | 7 | 9 | 9 | > 0.05 |
| Atrial fibrillation | 3 | 4 | 3 | > 0.05 |
| Cerebral infarction | 8 | 10 | 12 | > 0.05 |
| NIHSS | 10.25 ± 1.20857 | 9.88 ± 1.39404 | 9.80 ± 1.0000 | > 0.05 |

### 2.3. Observation items

The NIHSS score was measured in all the patients before treatment and 24 h, 1 day, and 7 days after treatment and the mRS score 90 days after treatment. The incidence of asymptomatic and symptomatic ICH was recorded on the basis of the craniocerebral SWI findings and clinical symptoms (an increase of more than 4 points in the NIHSS score indicates a worsened condition, while a decrease of more than 4 points indicates an obvious efficacy). A change from 0 to 1 point in the day-90 mRS score indicates good prognosis, while a change from 2 to 6 points indicates a bad prognosis.[17]

### 2.4. Statistical analysis

Data were analyzed using SPSS version 17.0. Measurement data were presented using $\bar{x} \pm s$. Data between two groups were compared using the t-test. Enumeration data were compared using the $\chi^2$ test. The difference was statistically significant when the p value was < 0.05.

## 3. Results

### 3.1. NIHSS score comparison

The NIHSS scores of Groups A and C decreased significantly at each time point after treatment compared with those before treatment; they were significantly lower than those in Group B ($p < 0.05$, Table 2). The difference in the NIHSS scores of Groups A and C among the time points after treatment was not significant ($p > 0.05$, Table 2).

### 3.2. Day-90 mRS score comparison

After 90 days of treatment, the mRS scores of Groups A and C were significantly lower than that of Group B ($p < 0.05$, Table 3).

### 3.3. Asymptomatic ICH incidence comparison

The asymptomatic ICH incidence in Groups A and C was significantly higher than that in Group B ($p < 0.05$, Table 4). No symptomatic ICH occurred in all groups.

**Table 2**
NIHSS score comparison before and after TT between different groups ( $\bar{x} \pm s$).

| Group | A (n = 20) | B (n = 25) | C (n = 25) | Tab value | Tac value |
|---|---|---|---|---|---|
| Before TT | 10.25 ± 1.2085 | 9.88 ± 1.3940 | 9.80 ± 1.0000 | 0.9377 ($p > 0.05$) | 1.3673 ($p > 0.05$) |
| One day after TT | 7.25 ± 0.9105 | 9.36 ± 1.1504 | 7.80 ± 1.1547 | 6.6910 ($p < 0.01$) | 1.7399 ($p > 0.05$) |
| Seven days after TT | 6.45 ± 0.6048 | 8.56 ± 1.1576 | 5.96 ± 0.9781 | 7.3747 ($p < 0.01$) | 1.9584 ($p > 0.05$) |
| 21 days after TT | 3.1 ± 1.3727 | 6.92 ± 0.9539 | 3.04 ± 1.6197 | 10.9980 ($p < 0.01$) | 0.1320 ($p > 0.05$) |

Note: Tab represents the t value obtained from the comparison between Group A and Group B; tac represents the t value obtained from the comparison between Group A and Group C.

**Table 3**
Day-90 mRS score comparison among three groups.

| Group | A | B | C | $X^2$ ab value | $X^2$ ac value |
|---|---|---|---|---|---|
| Case No. | 20 | 25 | 25 | | |
| Day-90 mRS | $1.65 \pm 0.8751$ | $2.20 \pm 0.8165$ | $1.68 \pm 1.0296$ | 2.1750 ($p < 0.05$) | 0.1037 ($p > 0.05$) |

Note: $X^2$ ab represents the $X^2$ value obtained from the comparison between Group A and Group B; $X^2$ ac represents the $X^2$ value obtained from the comparison between Group A and Group C.

**Table 4**
ICH incidence comparison of three groups.

| Group | A | B | C | $X^2$ ab value | $X^2$ ac value |
|---|---|---|---|---|---|
| Case No. | 20 | 25 | 25 | | |
| Asymptomatic ICH | 7 (35%) | 4 (16%) | 8 (32%) | 3.76470 ($p < 0.05$) | 0.76190 ($p > 0.05$) |
| Symptomatic ICH | 0 | 0 | 0 | | |

Note: $X^2$ ab represents the $X^2$ value obtained from the comparison between Group A and Group B; $X^2$ ac represents the $X^2$ value obtained from the comparison between Group A and Group C.

## 4. Discussion

AIS mostly results in local ischemic necrosis of the cerebral tissue, resulting from cerebrovascular occlusion and consisting of an infarction core and IP. Recently, researchers defined the IP as a reversible ischemic cerebral tissue area in the hypoperfusion area surrounding the ischemic infarction core.[18] Evidence-based medical studies demonstrated that intravenous TT using rt-PA could re-dredge the vessels blocked during the early stage of AIS and save the IP; this is currently the most efficient treatment against hyperacute ischemic stroke.[19,20] The IP involves cytotoxic cerebral edema, which will transform into vasogenic edema 3–4 h after ischemia. This short existence time restricts the clinical rt-PA application. Although the TW of intravenous TT has been increased to 3–4.5 h in the guidelines of the American Heart Association (AHA) and European Stroke Organization, as well as in the Chinese guideline for the treatment of AIS, which enabled many patients to receive TT, a large number of patients still cannot be treated within the TW, resulting in the development of functional neurological disorders. A recent study found that the IP involves a dynamic pathological process, which can transform to normal tissues if blood perfusion is restored on time after ischemia and to infarction regions if the ischemia lasts for some time.[21] A further study demonstrated that the existence of the IP depended not only on the duration of cerebral ischemia, but also on ischemic tolerance and collateral circulation.[22] Therefore, although the TW has already been exceeded in some patients, the IP could still be observed; they might lose the opportunity to receive TT and for their IP to be saved if they are excluded only by their stroke onset time. With the development of MRI technology and knowledge on the IP, researchers have realized that the pathological process of AIS varies among patients; the duration of IP existence may also vary owing to the differences in the underlying diseases, disease location, ischemic tolerance, and collateral circulation among patients. Moreover, PDM can be used to determine IP existence during stroke, leading to the proposal that it is more reasonable to change the traditional TW of intravenous TT to the necrotic TW of individual cerebral tissues for guiding the therapy.[23] Hence, the key point of this proposal is how to recognize the IP in time for TT in patients with a TW of more than 4.5 h. PDM is considered as the gold standard finding for judging the IP clinically. Tong et al. investigated patients with AIS who underwent PWI and DWI and illustrated that these were reliable for the diagnosis and determination of the prognosis of patients with cerebral infarction based on PDM.[24] Previous studies have demonstrated that the TT efficacy in patients with AIS during the early stage was remarkable when the PDM value was higher than 20%;[25] conversely, no therapeutic effect was observed when it was lower than 20%,[26] indicating the value of 20% as a reliable standard for the therapy. We also used this standard in our study, in which low-dose rt-PA was administered to the patients with a PDM value higher than 20% for intravenous TT; anti-thrombotic and lipid-lowering therapy were applied to those with a value lower than 20%. Moreover, to reduce the incidence of asymptomatic ICH, individual low-dose TT was performed in this study. Our results indicated that the NIHSS and mRS scores were not significantly different between the cases with the standard and broadened TWs. The grading of both thrombolytic groups was significantly better than that of the anti-thrombolytic group, indicating an obvious efficacy of the broadened-TW TT. There were seven cases of asymptomatic ICH in the broadened TW group, four cases in the anti-thrombolytic group, and eight cases in the standard TW group. This finding demonstrates a higher incidence of asymptomatic ICH in the thrombolytic group than in the anti-thrombolytic group, which indirectly illustrates the successful reperfusion with TT and improvement of clinical symptoms.[27] No symptomatic ICH was observed in neither group, probably resulting from the exclusion of patients with higher NIHSS scores, who require endovascular treatment, or from the administration of a low-dose thrombolytic drug.

Intravenous TT with a broadened TW for AIS under multimode MRI monitoring was proven to be effective and safe, without increasing the incidence of symptomatic or asymptomatic ICH; this may serve as a reliable screening and curing method for some patients with a broadened TW. However, further studies with larger sample sizes are needed to ensure the practical value of this study, considering that the case number herein was small, and patients with higher NIHSS scores, who require endovascular treatment, were excluded.

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## Conflicts of interest

The authors declare no conflict of interest.

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