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Observation of clinical efficacy of rt-PA intravenous thrombolytic treatment for patients combined with grade 0-1 diabetic foot by Wagner classification and acute ischemic stroke

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Abstract. – OBJECTIVE: To evaluate the safety and efficacy of rt-PA intravenous thrombolytic treatment for patients with diabetic foot (DF) and acute ischemic stroke.

PATIENTS AND METHODS: A retrospective analysis was performed on 76 patients admitted between June 2012 to December 2015 presenting with acute ischemic stroke and Grade 0-1 DF a (Wagner classification). The treatment group consisted of 44 patients who received rt-PA intravenous thrombolytic treatment, while 32 cases in the control group did not. Both groups received monitored dietary therapy and hypoglycemic drugs to control their blood glucose levels. In the treatment group, patients received rt-PA intravenous thrombolytic treatment 4.5h after the onset of ischemic stroke. Physical parameters like color change of sick-foot skin, conditions of ulcer concrescence, changes of skin temperature, and promotion of pain scores were observed in both the groups.

RESULTS: The improvement in the rt-PA intravenous thrombolytic treatment group was higher than that in general treatment group, and the difference between them had statistical significance ($p<0.01$). Though the improvement of foot symptoms of patients who received rt-PA intravenous thrombolytic was better than that of the control group; there was no obvious statistical difference in the incidence of adverse events between the treatment group and the control group.

CONCLUSIONS: rt-PA can reduce the level serum fibrinogen, promotes local microcirculation and nutrition metabolism of diabetic foot, and improve the clinical prognosis of patients with diabetic foot, but will not increase the incidence of adverse events at the same time.

Key Words:
rt-PA, Diabetic foot, Acute ischemic stroke, Thrombosis, Microcirculation.

Introduction

In recent years, the incidence of cerebral stroke in China increases at a rate of 8.70% annually[1]. It is reported that patients with cerebral stroke combined with type-2 diabetes account for 25.4% of the total stroke case, diabetic microangiopathy being the main reason of stroke. There are studies stating a relative risk of 2-3 times of acute stroke in diabetic patients when compared to non-diabetics[2]. The peripheral arterial damage associated with diabetes causes diabetic foot (DF)[3]. Early rt-PA intravenous thrombolytic treatment can significantly improve clinical prognosis in patients with acute ischemic stroke[4], but at the same time rt-PA activates fibrinolytic activity, which reduces procoagulant activity, increasing the risk of active bleeding[5]. Thus rt-TPA treatment for acute stroke in patients with the diabetic foot is still controversial. This study evaluates the safety and efficacy of rt-PA intravenous thrombolytic treatment in Grade 0-1 diabetic foot patients (Wagner classification[6]) presenting with acute stroke episode.

Patients and Methods

Patients

A retrospective analysis was performed on 76 patients with acute ischemic stroke and Grade 0-1 diabetic foot (DF) as classified by Wagner classification admitted to Neurological Department, Huanhu Hospital, Tianjin. The patients presenting within 4.5h after onset from June 2012 to December 2015 were a part of the study. The age range was between 62-80 years (average 71.2 years). There were 46 males and 30 females. The diabe-

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tic history ranged between 5 to 27 years (average 14.6 years), and the duration of the diabetic foot was from 6 months to 4 years. Fasting plasma glucose of patients was (12.2 ±3.96) mmol/L when they were admitted to the hospital. For patients in two groups, there was no statistical significance in gender, age, past medical history, severity of stroke, severity of diabetes, and grades of diabetic foot (p>0.05), as shown in Table I.

Diabetic foot is divided into 6 grades by Wagner classification of Diabetic Foot:

Grade 0: foot with risk factors of ulcer; no ulcer at present.

Grade 1: foot with superficial ulcer; no infection clinically.

Grade 2: foot with deep ulcer, often combined with cellulitis; no abscess or bone infection.

Grade 3: foot with deeper ulcer, accompanied by lesions of bone tissues, abscess or osteomyelitis.

Grade 4: foot with ischemic ulcer and circumscribed gangrene (toe, heel or dorsal forefoot).

Grade 5: gangrene of the whole foot.

Inclusion Criteria and Exclusion Criteria for Patients Undergoing Intravenous Thrombolysis

Criteria in reference of this study for patients undergoing intravenous thrombolysis refers to early treatment guidelines for acute ischemic stroke in 2013 American Heart Association/American Stroke Association (AHA/AHS)[7], and 2010 Diagnosis Guidelines for Acute Ischemic Stroke[8]. The details are as follows:

Inclusion criteria and exclusion criteria for patients undergoing rt-PA intravenous thrombolysis within 3h after onset:

Inclusion criteria: (1) age ≥18 years old; (2) the onset time ≤3h; (3) with definite neurological function impairment, and clinically diagnosed as acute ischemic stroke; (4) family members sign the informed consents.

Exclusion criteria: (1) previous medical history of intracranial hemorrhage; (2) medical history of head trauma or acute ischemic stroke in the last 3 months; (3) subarachnoid hemorrhage suggested by symptoms; (4) with artery puncture of non-compression parts in the last 7 days; (5) history of spinal cord operation, intracranial operation, etc.; (6) intracranial tumor, arteriovenous malformations, intracranial aneurysm; (7) with active internal bleeding in body, acute hemorrhagic diathesis, including but not limited to: 1) platelet count <100,000/mm^3 [100×109/L]; 2) treated with weight heparin within the last 48h, aPTT was higher than the upper limit of normal range; 3) taking oral anticoagulation currently; INR >1.5 or PT >15 seconds; 4) using direct thrombin inhibitors or direct factor Xa inhibitor, with increases of sensitive laboratory indexes [such as setting time of aPTT, INR, platelet counts and Ecarin clotting time (ECT); thrombin time (TT); or measurement of appropriate factor Xa]; 5) blood glucose concentration <50 mg/dL (2.7 mmol/L).

Inclusion criteria and exclusion criteria for patients undergoing rt-PA intravenous thrombolysis within 3-4.5h after onset:

Inclusion criteria: (1) with definite neurological function impairment, and clinically diagnosed as acute ischemic stroke; (2) before treatment, symptoms happened within 3-4.5h.

Exclusion criteria: (1) over 80 years old; (2) serious stroke (NIHSS scores >25); (3) taking oral anticoagulants, regardless of INR values; (4) with medical history of diabetes and ischemic stroke.

Methods of Intravenous Thrombolytic Treatment

According to clinical and laboratory confirmation of acute stroke and patients conforming to intravenous thrombolysis, convention oxygen inhalation was given, an intravenous pathway was established. Blood glucose levels, blood pressure, heart rate and other vital signs were monitored. For patients whose blood glucose ≥11.1 mmol/l, insulin was pumped to reduce blood glucose which was controlled between range of 7.8 to 10.3 mmol/l before thrombolysis. For patients whose systolic pressure ≥185 mmHg or diastolic pressure >110 mmHg, urapidil was slowly injected to reduce blood pressure which was controlled among 140-150/80-90 mmHg; oxygen saturation was maintained above 94%. rt-PA (specification: 20 mg and 50 mg) produced by Boehringer Ingelheim Co. (Berlin, Germany) was chosen. The medicine was given in compliance with the standard dose, 0.9 mg/kg (the maximum dose was 90 mg); 10% of total dose was used for intravenous bolus injection for 1 minute, and the rest 90% was diluted in 0.9% sodium chloride solution and used for intravenous pump dripping which was completed within 1 hour.

After thrombolysis, oxygen free radical was scavenged, cerebral circulation and metabolism were improved, and anti-arteriosclerosis treatment was carried out. Cerebral MRI, MRA and MR perfusion was re-exanimated conventionally 24 hours after thrombolysis. For patients who could not receive cerebral nuclear magnetism examination, cerebral CT, CTA and CT perfusion was performed. According to results of imaging examination, if patients

Table I. The comparisons of baseline data of the intravenous thrombolysis group and the non-intravenous thrombolysis group for diabetic foot.

Group	The treatment group (44)	The untreated group (32)
Recovery (%)	13 (29.5)	5 (15.6)
Effective (%)	21 (47.7)	14 (43.8)
Ineffective (%)	10 (22.7)	7 (21.9)
Aggravated (%)	0 (0)	6 (18.8)
Overall Response Rate (%)	34 (77.3)	19 (59.3)

in the intravenous thrombolysis group did not have hemorrhage or blood oozing 24 hours after thrombolysis, they were given 100 mg/day aspirin and 75 mg Gd clopidogrel and oral anti-platelet therapy. For patients in the control group, besides oxygen free radical was scavenged, cerebral circulation and metabolism was promoted, and anti-arteriosclerosis treatment was carried out, they were given oral anti-platelet therapy.

Efficacy Evaluation

Evaluation of clinical symptoms of stroke: NIHSS rating scales were used to assess conditions of neurologic functions in patients at time of admission and 7 days after treatment. Clinical prognosis at 3 months was evaluated by modified Rankin score. All evaluation and examinations were conducted by senior neurologists.

Evaluation of symptoms of diabetic foot: VAS rating scales, were used to assess pain rating in patients' feet at time of admission and 7 days after treatment. Front and back toe temperature and skin temperature, before and after treatment, were recorded to evaluate changes in skin temperature of patients. Changes in the diameters of eczema and ulcer of feet, and changes of skin color were measured to evaluate prognosis of patients' feet. The ratio of total scores after treatment to those before treatment was used to evaluate treatment efficacy.

Scoring Methods

i) Neurological function impairment Scoring criteria of National Health Institute Stroke Scale (NHISS) was taken.

ii) Neurological function prognosis Patients were followed up 90 days after onset, and modified Rankin score (mRS) was adopted to evaluate neurological function prognosis of patients. 0-2 points meant good neurologic prognosis, 3-5 points meant poor neurologic prognosis, and 6 points meant death.

iii) Pain of Diabetic feet (VAS rating scale was used to evaluate conditions of pain of sick feet): 0 points meant no pain, 2 points meant bearable mild pain, 4 points meant moderate pain for which painkiller is needed and 6 points meant severe pain needed to be treated with anesthetics.

iv) Changes of skin color: 0 points meant normal, 1 point meant that sick foot was dark red or pale occasionally, 2 points meant that sick foot was dark red or pale continuously or improvement did not happen, and 3 points meant that sick foot was deep purple.

v) Ulcer diameter: 0 points meant no ulcer, 1 point meant smaller ulcer area or scab, 2 points meant no improvement of ulcer area and 3 points meant larger ulcer area.

vi) Prognosis of diabetic foot: the ratio <0.3 was considered as recovery, 0.3-0.9 as effective, ratio of 0.9-1 as ineffective and the ratio >1 as aggravated.

Statistic Analysis

SPSS 19.0 software (IBM, Armonk, NY, USA) was used for statistical analysis. Enumeration data were expressed by the mean ± standard deviation (x-±s), and X2 test was adopted. The comparison of mean in different groups was tested by two independent sample *t*-test. $p < 0.05$ indicated that the difference was statistically significant.

Results

In this research, 76 patients with acute ischemic stroke and diabetic foot were treated in Neurological Department, Huanhu Hospital, Tianjin. Among these 76 patients, 44 (57.9%) received intravenous thrombolytic treatment, while 32 (42.1%) did not. For patients in two groups, the difference in the comparison of NHISS scores before and after thrombolysis had statistical significance ($p<0.05$), as shown in Table II.

Table II. NHISS scores.

Group	The thrombolysis group	The non-thrombolysis group
Before treatment	10±3	9±3
After treatment	7±4	10±3
t value	3.207	2.367
p value	0.002	0.023

Table III. Evaluation on prognosis of diabetic foot.

Item	The treatment group n=44	The untreated group n=32	*p* value
Demographic characteristics			
Gender, male (%)	24 (54.5)	22 (68.8)	0.617
Age x ± s	64.2±12.7	63.4±12.5	0.589
NHISS	10±3	9±3	0.914
Risk factors			
Coronary heart disease n (%)	15 (34.1)	9 (28.1)	0.559
Hypertension n (%)	28 (63.6)	20 (62.5)	0.552
Hyperlipemia n (%)	17 (38.6)	9 (28.1)	0.315
Drinking n (%)	18 (40.9)	12 (37.5)	0.412
Smoking n (%)	22 (50.0)	17 (53.1)	0.120
Previous ischemic stroke or TIA n (%)	10 (22.7)	7 (21.9)	0.817
Admission blood pressure			
SBP(mmHg)x ± s	163.9±21.2	162.6±27.1	0.285
DBP(mmHg)x ± s	91.2±12.1	89.7±14.5	0.151
Laboratory examination			
White blood count (×109/L) x ± s	8.9±3.4	8.6±3.0	0.522
Total cholesterol (mmol/L) x ± s	5.1±0.9	5.4±1.3	0.560
Triglycerides (mmol/L) x ± s	1.5±0.8	1.7±0.9	0.308
High-sensitivity C-reactive protein (mg/L) x ± s	5.6±1.8	5.7±1.7	0.814
Blood sugar level when admitted to hospital (mmol/L) x ± s	8.1±3.9	7.8±3.2	0.224

Clinical Prognosis of Symptoms of Diabetic Foot

For patients with acute ischemic stroke and diabetic foot, the comparison of clinical prognosis of diabetic foot in the intravenous thrombolysis group and the non-thrombolysis group was listed in Table III and Table IV. In these two groups, symptoms of diabetic foot in the intravenous thrombolysis group before and after treatment had a statistical significant improvement at 7 days ($p<0.01$). As for VAS scores and improvement of skin temperature, prognosis of the intravenous thrombolysis group was better than that of the control group ($p<0.05$).

Improvement of Symptoms of Patients with Stroke after the Intravenous Thrombolytic Treatment

The differences in NHISS scores of the thrombolysis group and the control group has statistical significance ($p<0.05$). According to statistical data analysis, the prognosis for 3 months of patients undergoing intravenous thrombolytic treatment was better than that of patients who did not. The mortality of patients undergoing intravenous thrombolytic treatment was lower than that of patients who did not. At the 3rd month, prognosis of patients with acute ischemic stroke and diabetic foot who underwent intravenous thrombolytic

Table IV. Changes in self-conscious symptoms of patients before and after intravenous thrombolytic treatment.

	VAS scores		Color of skin		Ulcer		Increase of skin temperature	
Group	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
The thrombolysis group	2.76±0.40	1.42±0.29	1.50±0.88	0.54±0.62	1.08±1.11	0.24±0.41	1.79±1.25	0.35±0.49
The control group	2.31±0.32	2.19±0.21	1.54±0.92	1.06±0.14	1.27±1.06	1.01±0.62	1.81±1.06	0.92±0.88

Table V. The comparison of mRS scores 90d after patients treated with thrombolytic treatment.

Group	The thrombolysis group	The non-thrombolysis group
Good prognosis	29 (65.9)	10 (31.3)
Poor prognosis	15 (34.1)	20 (62.5)
Death	0 (0)	2 (6.3)
Total	44	32

treatment was better than those of patients who did not. Meanwhile, the mortality of patients with stroke and diabetic foot who underwent intravenous thrombolytic treatment was lower than that of patients who did not. mRS scores at 3 months were listed in Table V.

Discussion

Since Alteplase (rt-PA) intravenous thrombolytic treatment was allowed by FDA to treat acute ischemic stroke (AIS) in 1996, life quality of patients with acute ischemic stroke has improved a lot, and fatality rate and disability rate also reduced[9,10]. However, there are few relevant studies on patients with Grade 0-1 diabetic foot by Wagner classification and acute ischemic stroke who were treated with intravenous thrombolytic treatment. In this research, a retrospective analysis was performed on patients with acute ischemic stroke and Grade 0-1 diabetic foot by Wagner classification to evaluate safety and efficacy of rt-PA intravenous thrombolytic treatment. It was found that the improvement rate of diabetic foot for patients with Grade 0-1 diabetic foot after intravenous thrombolytic treatment was higher than that in the control group, and no adverse events happened.

There are 2%-37% patients with diabetes having ulcers on lower legs[11]. Diabetic foot is caused by lesion of diabetic peripheral vessels. High blood glucose will lead to endocrine and metabolic disorders, reduces vascular elasticity, and promotes the progress of atherosclerosis; continuous hemodynamic abnormality will lead to damages of vascular structures, vascular sclerosis and thickened basement membrane, causing vascular endothelial injury[12,13]. In blood vessels, venous thrombosis form gradually, leading to blocked circulation of blood pressure, microcirculation occlusion, and ischemia in local tissues. As microcirculatory disturbance progresses, hypoxia and ischemia in local tissues become more serious, leading to ischemic necrosis of local tissues, and diabetic foot further[14]. Most of the previous studies[15] regarded diabetic foot as clinical manifestation of severe diabetes and analyzed clinical prognosis of intravenous thrombolysis by using it as an independent risk factor of vascular risks. Only two studies explored prognosis and safety of intravenous thrombolytic treatment for patients with diabetic foot and acute ischemic stroke. But in these two studies the sample size was small and the criteria to define the study group was different.

Some studies suggest that during the course development of diabetes, microcirculatory disturbance occurs early. The hemodynamic abnormality is an important manifestation of microcirculatory disturbance. Arenillas et al[16] found that severe diabetes was related to poor prognosis after intravenous thrombolytic treatment. This study believed that in patients with uncontrolled diabetes failure of anti-thrombolytic agent occurs as the artery occlusion in the brain obstructed thrombolytic drugs to dissolve thrombus. After veins had been given rt-PA intravenous thrombolytic treatment, if the detection by transcranial Doppler found that arterial occlusion still existed, it can be assumed that resistance to thrombolytic agents happened. Meanwhile, the author of this study suggested that the incidence of resistance to thrombolytic agents for females was higher than that for males[17].

This research found that the ratios of short-term and long-term prognosis for the rt-PA intravenous thrombolytic treatment were higher than those of the normal treatment group, and the difference between two groups had statistical significance ($p<0.01$). For patients with diabetic foot who had undergone rt-PA intravenous thrombolytic treatment, there was increased arterial pulse of dorsal feet, good ulcer healing, and pain relief. This may be because rt-PA can selectively combine with plasminogen and fibrin on the surface of thrombus to form compounds; during this period, plasminogen is transformed to plasmin; therefore, it can dissolve thrombus, which effectively improves blood flow of microcirculation, promotes blood return, reduces intravenous extravasation of blood and relieve limb swelling; so healing conditions of ulcer and self-conscious symptoms of patients were improved. Studies manifest that the half-life of rt-PA is 4-8 minutes, and it has little pharmaco-

logical effects on free plasmin in plasma, so it will not cause systemic fibrinolysis.

This research also found that there was no statistical difference in the incidence of adverse events for patients in the treatment group and the control group. In the treatment group, overall response rate was 77.3%, and clinical symptoms did not worsen. We assumed that diabetic foot should not be the contraindication of intravenous thrombolytic treatment; what's more, after patients received intravenous thrombolytic treatment, their foot symptoms improved obviously, and no adverse events happened.

Conclusions

Taken above, intravenous thrombolytic treatment should be used more widely as it can benefit more patients. However, because of different research methods and different sample size, this research could not be compared with others. We also realized the limitations. More related information should be collected for analysis. Meanwhile, this research did not deeply analyze insulin resistance, so it is lack of related persuasive theories.

Conflicts of interest

The authors declare no conflicts of interest.

References

1) Bejot Y, Catteau A, Caillier M, Rouaud O, Durier J, Marie C, Di Carlo A, Osseby GV, Moreau T, Giroud M. Trends in incidence, risk factors, and survival in symptomatic lacunar stroke in Dijon, France, from 1989 to 2006: a population-based study. Stroke 2008; 39:1945-1951.
2) Donnell MJ, Xavier D, Liu L. Risk factors for ischemic and in-tracerebral haemorrhagic stroke in 22 countries (the INTESTEOKE study): a case-control study. Lancet 2010; 376: 112-123.
3) Lavery LA, Armstrong DG, Wunderlich RP, Tredwell J, Boulton AJ. Diabetic foot syndrome: evaluating the prevalence and incidence of foot pathology in Mexican Americans and non-Hispanic whites from a diabetes disease management cohort. Diabetes Care 2003; 26: 1435-1438.
4) Molina CA, Alexandrov AV and Demchuk AM. Improving the predictive accuracy of recanalization on stroke outcome in patients treated with tis-sue plasminogen activator. Stroke 2004; 35: 151-156.
5) Chen Y, Li CH, Wang YX, Zhang CH, Dong Z, Zhang FF, Wang JH, Zhang PL. Safety and effectiveness of intravenous thrombolysis with recombinant tissue plasminogen activator in eighty years and older acute ischemic stroke patients. Eur Rev Med Pharmacol Sci 2015; 19: 1852-1858.
6) Calhoun JH, Cantrell J, Cobos J, Lacy J, Valdez RR, Hokanson J, Mader JT. Treatment of diabetic foot infections: Wagner classification, therapy, and outcome. Foot Ankle 1988; 9: 101-106.
7) 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.
8) Schellinger PD, Bryan RN, Caplan LR, Detre JA, Edelman RR, Jaigobin C, Kidwell CS, Mohr JP, Sloan M, Sorensen AG, Warach S. Evidence-based guideline: The role of diffusion and perfusion MRI for the diagnosis of acute ischemic stroke: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2010; 75: 177-185.
9) Wang HR, Chen M, Wang FL, Dai LH, Fei AH, Liu JF, Li HJ, Shen S, Liu M, Pan SM. Comparison of therapeutic effect of recombinant tissue plasminogen activator by treatment time after onset of acute ischemic stroke. Sci Rep 2015; 5: 11743.
10) Zhang B, Sun XJ, Ju CH. Thrombolysis with alteplase 4.5-6 hours after acute ischemic stroke. Eur Neurol 2011; 65: 170-174.
11) Levine SR, Khatri P, Broderick JP, Grotta JC, Kasner SE, Kim D, Meyer BC, Panagos P, Romano J, Scott P. Review, historical context, and clarifications of the NINDS rt-PA stroke trials exclusion criteria: Part 1: rapidly improving stroke symptoms. STROKE 2013; 44: 2500-2505.
12) Zhang PY. Cardiovascular disease in diabetes. Eur Rev Med Pharmacol Sci 2014; 18: 2205-2214.
13) Marigo L, Cerreto R, Giuliani M, Somma F, Lajolo C, Cordaro M. Diabetes mellitus: Biochemical, histological and microbiological aspects in periodontal disease. Eur Rev Med Pharmacol Sci 2011; 15: 751-758.
14) Lawall H, Amann B, Rottmann M, Angelkort B. The role of microcirculatory techniques in patients with diabetic foot syndrome. VASA 2000; 29: 191-197.
15) Fang F, Wang YF, Gu MY, Chen H, Wang DM, Xiao K, Yan S, Yao LL, Li N, Zhen Q, Peng YD. Pedobarography–a novel screening tool for diabetic peripheral neuropathy? Eur Rev Med Pharmacol Sci 2013; 17: 3206-3212.
16) Arenillas JF, Sandoval P, Perez de la Ossa N. Metabolic syndrome is associated with a higher resistance to IV thrombolysis for acute ischemic stroke in women than in men. Stroke 2009; 40: 344-349.
17) Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D, Grotta JC, Albers GW, Kaste M, Marler JR, Hamilton SA, Tilley BC, Davis SM, Donnan GA, Hacke W, Allen K, Mau J, Meier D, Del ZG, De Silva DA, Butcher KS, Parsons MW, Barber PA, Levi C, Bladin C, Byrnes G. Time to treatment with intravenous alteplase and outcome in stroke: An updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet 2010; 375: 1695-1703.