

Analysis of related factors of orolingual angioedema after rt-PA intravenous thrombolytic therapy

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Abstract. – **OBJECTIVE:** Orolingual angioedema (OA) is a rare clinical complication with a potentially fatal risk that occurs after the intravenous application of alteplase (rt-PA) in patients with acute ischemic stroke. The purpose of this work is to investigate the related factors of OA in patients with acute ischemic stroke after the administration of intravenous thrombolytic therapy, to improve the predictive ability of OA during intravenous thrombolytic therapy, and to reduce the prevalence of complications.

PATIENTS AND METHODS: We recruited 1223 cases of patients with acute ischemic stroke that were treated in the Department of Neurology No. 4 of the Tianjin Huanhu Hospital from June 2014 to April 2015. The clinical manifestations of rt-PA related OA were recorded, the clinical prevalence was counted, related factors of OA after intravenous thrombolytic therapy were analyzed, and the risk assessment of rt-PA related OA was conducted.

RESULTS: 14 cases of patients developed OA, with a prevalence rate of 1.14%. Among them, 5 had a history of urticaria, 4 of drug allergy, and 3 of food allergy. Among the 14 cases of patients, 10 developed OA in the process of intravenous thrombolysis and 4 after intravenous thrombolysis, 12 showed lip edema, 9 showed extensive swelling of tongue, 3 showed swelling of lateral tongue, 3 were complicated by respiratory distress, 10 showed infarction in the middle cerebral artery territory, and 6 had previously been given oral ACEI drugs.

CONCLUSIONS: Orolingual angioedema is a rare complication that occurs after rt-PA intravenous thrombolytic therapy; when serious, it may endanger a patient's life. If patients take an oral hypotension such as ACEI drugs before the onset of OA, they have a history of allergies, or the lesion is an infarction in the dominated area of the middle cerebral artery, the risk of OA after rt-PA intravenous thrombolytic therapy will be in-

creased. The prevalence of OA should be monitored during the rt-PA intravenous thrombolytic therapy process; timely detection and early intervention should be conducted, which can avoid serious adverse consequences.

Key Words:

Recombinant tissue plasminogen activator, Orolingual angioedema, Intravenous thrombolysis, Acute ischemic stroke.

Introduction

Since 1996, when the American FDA approved a Recombinant Tissue Plasminogen Activator (rt-PA) to be put into intravenous thrombolytic therapy to treat acute ischemic stroke (AIS), intravenous thrombolysis is one of the most effective methods for the treatment of acute ischemic stroke, and it can significantly improve the clinical prognosis. The treatment effects of rt-PA in acute ischemic stroke through intravenous thrombolysis have been supported by many large clinical studies¹. With the continuous promotion and further study of rt-PA intravenous thrombolytic therapy, some post-treatment complications caught the attention of clinicians and researchers. In addition to symptomatic intracranial hemorrhage, which clinicians are most concerned about, fatal orolingual angioedema (OA) should also not be ignored. Rt-PA related OA is characterized by angioedema in the face, tongue, throat, neck, and other parts of the patients with acute ischemic stroke that are treated with intravenous thrombolysis during or after thrombolysis, and it usually manifests as transient swelling in the tongue, lips,

and throat. It may cause airway obstruction and dyspnea, and may endanger the life of patients. It is a transient and rare clinical complication, but might potentially threaten a patients' life². According to clinical reports³⁻⁷, the prevalence rate of rt-PA related OA ranges from 0.89% to 7.90%. Therefore, understanding the related factors of rt-PA related OA, early detection, and timely intervention can reduce and prevent the occurrence of adverse consequences, which is very important to clinical work. This study retrospectively analyzed cases of orolingual angioedema developed in patients with acute ischemic stroke after intravenous thrombolytic therapy and discussed the related factors of orolingual angioedema during and after the process of intravenous thrombolytic therapy so as to reduce the occurrence of complications and improve the clinical prognosis of patients.

Patients and Methods

Patients

We retrospectively analyzed 1223 cases of patients with acute ischemic stroke that were treated in the Department of Neurology No. 4 of Tianjin Huanhu Hospital from June 2014 to April 2015. The onset time of all patients was within 4.5 h, and they received rt-PA intravenous thrombolytic therapy. This study was approved by the Ethics Committee of Tianjin Huanhu Hospital. Signed written informed consents were obtained from the patients and/or guardians.

Inclusion and Exclusion Criteria for Patients with Intravenous Thrombolysis

Inclusion and exclusion criteria of patients with intravenous thrombolysis refer to the early treatment guidelines of 2013 American Heart Association/Stroke Association (AHA/ASA)⁸ for patients with acute ischemic stroke and 2010 Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke in China⁹. The inclusion and exclusion criteria differed for patients who received rt-PA intravenous thrombolysis with disease onset within 3 h and for those who received the therapy with 3-4.5 h after onset. The criteria for patients who received therapy with 3 h are as follows. Inclusion criteria: (1) patients are 18 years old or older; (2) disease onset time was less than 3 h; (3) presents with clear neurologic deficits and who were clinically diagnosed with acute ischemic stroke; (4) informed consent was

obtained from patient and family. Exclusion criteria: (1) patients with previous intracranial hemorrhage history; (2) patients with a history of head trauma or ischemic stroke in recent 3 months; (3) patients whose symptoms suggested subarachnoid hemorrhage; (4) patients with arterial puncture in incompressible parts in the past 7 days; (5) patients with a surgical history in the spinal cord, intracalvarium, and other parts; (6) patients with intracranial tumor, arteriovenous malformation, and intracranial aneurysms; (7) patients with active internal hemorrhage and acute hemorrhagic diathesis, including but not limited, to: (1) platelet counts $< 100000/\text{mm}^3$ ($100 \times 10^9/\text{L}$); (2) patients received heparin therapy within 48 h, and aPTT was higher than the upper limit of the normal range; (3) patients were taking oral anticoagulants and $\text{INR} > 1.5$ or $\text{PT} > 15$ s; (4) patients were using direct thrombin inhibitor or direct factor Xa inhibitors, and sensitive laboratory indicators increased [such as aPTT, INR, platelet counts, and Ecarin Clotting Time (ECT); thrombin time (TT); or proper factor Xa determination]; (5) the blood glucose concentration was less than 50 mg/dL (2.7 mmol/L). The inclusion and relative exclusion criteria of patients with rt-PA intravenous thrombolysis within 3-4.5 h after the onset are as follows. Inclusion criteria: (1) patients must have clear neurological impairment and were clinically diagnosed with acute ischemic stroke; (2) patients whose symptoms occurred between 3-4.5 h before the treatment. The relative exclusion criteria: (1) patients age > 80 years old; (2) patients with severe stroke (NIHSS > 25 points); (3) patients taking oral anticoagulants, regardless of INR value; (4) patients with a history of diabetes mellitus and ischemic stroke at the same time.

Intravenous Thrombolytic Therapy

After clinical and laboratory assessment, and after admission to the hospital, patients who were in line with intravenous thrombolysis conducted routine oxygen inhalation, establishment of venous access, laboratory monitoring of blood glucose, blood pressure monitoring, heart rate, and other vital signs. Patients whose blood glucose levels were greater than or equal to 11.1 mmol/l were given intravenous infusion of glucose insulin (Novo Nordisk, Copenhagen, Denmark) in order to control the blood glucose before thrombolysis in 7.8-10.3 mmol/l. If the systolic blood pressure was greater than 185 mmHg or diastolic blood pressure was greater than 110 mmHg, intravenous urapidil was used to slowly

reduce the blood pressure and control it within 140-150/80-90 mmHg. Oxygen saturation of the blood remained above 94%. Drugs adopted rt-PA produced by Germany's Boehringer Ingelheim Company (Ingelheim am Rhein, Germany) (specification: 20 mg and 50 mg), and doses were in accordance with the 0.9 mg/kg standard dose (maximum dose was 90 mg), including 10% of the total amount in the peripheral vein bolus for 1 min, with the remaining 90% diluted in 0.9% sodium chloride solution, and 1 h of intravenous infusion pump was completed. 24 h after thrombolysis, a routine review was conducted in cranial MRI, MRA, and PWI perfusion. For patients who could not receive cranial magnetic examination, CT, CTA, and CTP perfusion were detected. 24 h after thrombolysis, if no bleeding and errhysis were observed in imaging findings of patients in intravenous thrombolysis group, they were given 100 mg qd aspirin, 75 mg qd combined clopidogrel, and oral anti-platelet aggregation therapy^{10,11}.

Clinical Date of rt-PA Related OA

The related factors were collected. They included age, gender, vascular risk factors, medical history of antihypertensive drugs and allergy, stroke parts, time from the onset to the treatment, admission blood pressure and NIHSS scores when admitted and discharged. Besides, the time from the application of rt-PA to the onset of OA, relationship between OA and infarction parts, OA parts, symptomatic treatment and the process of developing OA, were recorded.

Statistical Analysis

SPSS 21.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for data analysis. The measurement data are expressed as mean±standard deviation. Two independent samples were chosen to compare the mean values of different groups using the *t*-test. The *p*-value < 0.05 indicates a statistical difference.

Results

Demographic Information and Clinical Features of Patients with OA

Among 1223 cases of patients with acute ischemic stroke who received rt-PA intravenous thrombolysis, 14 cases of patients developed OA with a prevalence of 1.14%. It showed no significant statistical difference in gender, age of the onset of OA, admission blood pressure and

NIHSS scores, time from the onset to intravenous thrombolysis, and NIHSS scores when discharged between patients with OA and patients without OA (Table I).

Clinical Features and Treatment of Patients with OA

Among 14 cases of patients with OA, 5 cases had the medical history of urticaria, 4 of drug allergy, and 3 of food allergy. The time from the application of rt-PA to the development of OA was 38.90 min. Among them, 10 developed OA in the process of intravenous thrombolysis and 4 after intravenous thrombolysis; 12 showed edema, 9 showed swelling of bilateral tongue, 3 showed swelling of lateral tongue, 3 were complicated with respiratory distress, and 2 developed urticaria at the same. All the 14 cases showed no sign of tachycardia and low blood pressure. Besides, 10 cases showed infarct lesion in the middle cerebral artery territory, 2 in the brain stem, and 2 in the thalamus. Among them, swelling of lateral tongue and ischemic lesion side of 2 cases were the same and 1 was the opposite. Without the performance of endotracheal intubation and tracheotomy, the edema subsided completely within 24 h after all patients were given anti-allergic treatment by using dexamethasone and diphenhydramine (Table II).

Table I. Demographic information and clinical data of patients treated with Rt-PA intravenous thrombolysis.

Items	No. (%)
Age (years old), ($\bar{x} \pm s$)	62.2 ± 8.7
Male	898 (73.4)
Female	325 (26.6)
Risk factors no. (%)	
Diabetes mellitus	465 (38.0)
Hypertension	782 (69.9)
Hyperlipemia	506 (41.4)
Previous ischemic stroke or TIA	135 (11.0)
Atrial fibrillation	232 (20.0)
Coronary heart disease	758 (62.0)
Smoking history	1051 (85.9)
Drinking history	408 (33.4)
Laboratory examination	
Blood glucose when admitted to hospital (mmol/L), ($\bar{x} \pm s$)	7.4 ± 2.2
White blood cells count ($\times 10^9/L$), ($\bar{x} \pm s$)	8.9 ± 3.4
Total cholesterol (mmol/L), ($\bar{x} \pm s$)	7.4 ± 2.2
Triglyceride (mmol/L), ($\bar{x} \pm s$)	7.4 ± 2.2
Hyper-sensitive C reactive protein (mg/L), ($\bar{x} \pm s$)	7.4 ± 2.2
NIHSS scores when admitted to hospital, ($\bar{x} \pm s$)	8 ± 5

Table II. Clinical data of patients with OA related rt-PA (no. = 14).

Items	No. (%)
Gender	
Male	6 (42.9)
Female	8 (57.1)
Medication history of hypertension n (%)	
ACEI drugs	6 (42.9)
ARB drugs	3 (21.4)
β blocker	6 (42.9)
CCB drugs	6 (42.9)
Diuretics	2 (14.3)
Allergic history	
History of urticaria	5 (35.7)
History of drug allergy	4 (28.6)
History of food allergy	3 (21.4)

Correlation Between OA and the Use of Antihypertensive Drugs Before Stroke

Among 1223 patients enrolled, 558 cases (45.63) were diagnosed with hypertension, 424 of which had previously been given oral antihypertensive drugs (34.67%), and 134 patients had an unclear history of drug use (24.01%). All antihypertensive drugs given are as follows: 42 cases of ACEI drugs (9.91%), 190 cases of ARBs drugs (44.81%), 238 cases of β -blockers (56.13%), 250 cases of CCB drugs (58.96%), 160 cases of diuretics (37.74%), and 46 cases of other antihypertensive drugs (10.85%). In the 14 cases of patients with OA, 6 cases had previously been given oral ACEI drugs (Enalapril, Captopril, and Fosinopril), 3 given oral ARBs drugs (Irbesartan and Valsartan), 6 given oral CCB drugs (Amlodipine and Nifedipine) and 2 given oral diuretics (Indapamide and Hydrochlorothiazide). We found that the risk of taking ACEI drugs on the occurrence of rt-PA related OA was higher than taking non-ACEI drugs, and the comparison of both suggested statistical difference (Table III).

Discussion

Since 1996, the American FDA approved alteplase (rt-PA), which was put into intravenous thrombolytic therapy in order to treat acute ischemic stroke (AIS). It significantly improved the quality life of AIS patients and reduced the mortality and morbidity of patients. However, with the universal application of the alteplase, its side effects also raised people's concern. Apart from the risk of a well-known intracranial hemorrhage, allergic reactions, angioedema, and other adverse reactions have gradually been taken seriously by people; clinicians must not ignore OA (orolingual angioedema). Rt-PA related OA refers to angioedema in face, tongue, throat, neck, and other parts of AIS patients during or after intravenous thrombolysis. Although it is short, it is potentially a rare life-threatening clinical complication². This investigation found that the prevalence of rt-PA related OA patients with acute ischemic stroke was 1.14%, compared with previous studies of the prevalence of rt-PA related OA 0.89%-7.90³⁻⁷ which were similar to our findings. Meanwhile, we found that the prevalence of rt-PA related OA in China was lower than the prevalence in the Caucasian population (1.2-5.1%)^{12,13}. rt-PA related OA is also related to different genetic and racial tendencies. Gene polymorphisms may lead to a lack of C1 esterase, thereby causing excessive generation of bradykinin. Genetic cofactors can also increase the susceptibility of rt-PA related-OA¹⁴. Currently, possible influential factors and pathogenesis for rt-PA related OA remain unclear. This work found that patients with acute ischemic stroke have a higher risk of OA than those with acute myocardial infarction after rt-PA intravenous thrombolysis¹⁴, which is consistent with the reports worldwide. One study¹⁵ found that ischemic lesions blocking the autonomic nervous pathways can directly lead to the occurrence of OA, which may be related to the principle

Table III. The risk factors of different antihypertensive drugs and the occurrence of rt-PA related OA.

	OA		Relative risks
	Occurrence (no. = 14, %)	Nonoccurrence (no. = 424, %)	
ACEI	6 (42.86)	42 (9.91)	4.32
ARBs	3 (21.43)	190 (44.81)	0.47
β -blockers	6 (42.86)	238 (56.13)	0.76
CCB drugs	6 (42.86)	250 (58.96)	0.73
Diuretics	2 (14.29)	160 (37.74)	0.38

of anatomy. In this study, 10 cases of patients showed infarct lesion in the middle cerebral artery territory. Among them, swelling of lateral tongue and ischemic lesion side of 2 cases were the same, and 1 was the opposite, and 7 showed bilateral tongue angioedema. Hill et al¹⁵ found that, when compared to ischemia of other parts, ischemia in the insula and frontal parts have a higher risk of rt-PA related OA. Due to the insular cortex dysfunction of the opposite side, it caused autonomic nervous system dysfunction and the development of OA¹⁵. In this research, 64.29% of patients had a history of allergy, manifesting as urticaria, food allergy or drug allergy. Among them, OA and urticaria occurred in 2 cases after the intravenous infusion of rt-PA at the same time. Drug-related angioedema can be divided into two types: allergic and non-allergic angioedema. Allergic edema is a mast cell degranulation mediated by immunoglobulin, which is usually expressed as urticaria. In contrast, the non-allergic reaction occurs due to the production and accumulation of a large number of inflammatory cytokines¹⁶. Studies^{17,18} have reported that immunoglobulin E with rt-PA activity in the serum of one patient has been detected, which shows that although rt-PA is an endogenous protein, it also has a certain antigenicity. ACEI is one of the most common clinically used antihypertensive drugs. Clinical studies indicate that when compared to other antihypertensive drugs, ACEI induces OA at a higher rate. The prevalence rate is 3.56 times than that of other drugs¹⁹, considering that the application of ACEI antihypertensive drugs is a major induction factor for rt-PA related OA. This is similar to the findings of this work, since the risk of taking ACEI drugs on the occurrence of rt-PA related OA was higher than taking non-ACEI drugs. Under normal physiological condition, the major metabolic enzymes in bradykinin include aminopeptidase P, kinase I and II, among which kinase II is the main catabolic enzyme, also known as angiotensin-converting enzyme (ACE). When there is not enough ACE in the human body, bradykinin is converted by kinase I to arginine-BK, which is not easily removed through metabolism¹¹. Therefore, researchers^{6,7,20,21} believe that the administration of ACEI drugs orally can inhibit the excitation of kinase, resulting in heavy accumulation of bradykinin in the body, which may stimulate angioedema. Also, after the application of rt-PA in the vein, the pathway of enzymatic bradykinin can be activated, thus leading to the generation of bradykinin in the

body²². Therefore, researchers^{6,7,15} propose that enhancing the activity of bradykinin due to ACEI drugs may increase the risk of OA. Furthermore, among all types of antihypertensive drugs, Chinese people use more ARB drugs than ACEI drugs^{23,24}. It is reported that ARB drugs can also increase the levels of bradykinin^{25,26}. In our research, 3 patients suffered from rt-PA related OA after taking ARB drugs orally. Therefore, further study should be made to investigate whether ARB drugs can induce OA. Currently, antihistamine drug or glucocorticoids are provided for the treatment of rt-PA related OA, but once there are life-threatening symptoms like laryngospasm or anaphylactic shock, the infusion of rt-PA should be ceased and any changes must be closely observed²⁷. In this study, 14 cases of patients with OA were given hormone and antihistamine, and their edema was alleviated completely. Some application of drug treatment can also depend on our experience, including antihistamine drugs, glucocorticoid, and adrenaline²⁸. Although these drugs can't change the concentration of bradykinin, they still successfully cure rt-PA related OA, both in this research and other clinical reports^{7,15,27,29}. Thus, once there are evident clinical symptoms of allergic vascular edema, active drug intervention should be taken in time⁷. The application of tracheal intubation lies on the organ of allergic edema and the speed of progression of illness. The study also has some limitations. Firstly, the drug-taking history of 24.01% of selected patients are unspecified, which may underestimate the prevalence rate of rt-PA related OA induced by ACEI. Secondly, the utilization of ACEI drugs among Asian people is very low. Thus, our results cannot completely evaluate the risk of ACEI drugs to OA.

Conclusions

The prevalence rate of rt-PA related OA is 1.14%. The administration of ACEI drugs orally before thrombolysis, previous history of allergy, and dominated area of artery infarction in brain will increase the risk of rt-PA related OA. Those who have taken ACEI should be given intensive care in the rare case that rt-PA related OA may threaten their health.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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