

Analysis on the correlation factors for hemorrhagic transformation after intravenous thrombolytic therapy

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Abstract. – OBJECTIVE: To examine the correlation factors for hemorrhagic transformation after intravenous thrombolytic therapy, so as to improve the forecast about hemorrhagic transformation in the process of thrombolysis, and provide theoretical basis for prognosis of the patients.

PATIENTS AND METHODS: A total of 1223 patients with intravenous thrombolytic therapy including NIHSS score before intravenous thrombolytic therapy and MRS score by follow-up of three months after intravenous thrombolytic therapy were enrolled in this study, and related clinical data were collected. t test, 2 test and logistic regression analysis were used to find the correlation factors for hemorrhagic transformation.

RESULTS: Single-factor analysis found hypertension, diabetes mellitus, history of stroke and collateral circulation insufficiency had statistical significances between each type of hemorrhage group groups. Amongst of the history of hypertension, diabetes and stroke was correlation factor for prognosis.

CONCLUSIONS: Intravenous thrombolysis hemorrhagic transformation associated with these factors including the vessel wall, blood composition and biochemical markers.

Key Words:

Acute cerebral infarction, rtPA, Intravenous thrombolysis, Thrombolytic therapy.

Introduction

The incidence of stroke in China is increasing at a rate of 8.7% every year. The World Health Organization predicts that such a rising trend of the stroke patients would last for 30 years¹. Nowadays, the treatment for acute cerebral infarction is still far from dealing with the challenges of cerebral infarction, and the actual rate

of thrombolysis is very low. The rate of thrombolysis in ischemic stroke in China is only 1.13%, far less than the 10% in developed countries^{2,3}.

The time window of thrombolytic therapy in stroke in 2012 was as follows: FDA approved that rtPA venous thrombolytic therapy within three hours after onset was the only approved drug treatment up till now⁴. The stroke guides of various countries have recommended that acute ischemic stroke patients with the onset of disease within 4.5 hours should be treated with rtPA intravenous thrombolysis (China urokinase within 6 hours)⁵. Pathophysiological window (imaging guided thrombolysis): abnormal signal of T2, and FLAIR represented that the blood brain barrier was broken, and the duration of disease exceeded six hours. A high signal on the head nuclear magnetism DWI represented cytotoxic edema^{6,7}.

The biggest risk of intravenous thrombolysis was the occurrence of hemorrhagic transformation. When the time and pathophysiological window reached different conclusions on estimating whether thrombolysis could occur or not, it would interfere with the clinical intravenous thrombolytic therapy. Risk evaluation on the hemorrhagic transformation of acute ischemic stroke intravenous thrombolysis was an important bottleneck that would restrict the smooth carrying out of intravenous thrombolysis.

In this study, we have made a retrospective summary on the information of acute ischemic stroke patients after intravenous thrombolytic therapy, analyzed correlation factors for hemorrhagic transformation after alteplase intravenous thrombolytic therapy, so as to improve the forecast about hemorrhagic transformation in the process of thrombolysis, to minimize the risk of thrombolysis and to improve the prognosis of patients.

Patients and Methods

Clinical Samples

Enroll a total of 1223 patients who were undergoing intravenous thrombolytic therapy of acute ischemic stroke in Neurology Department of Tianjin Huanhu Hospital from June 2012 to April 2014, amongst which there were 898 males and 325 females. No hemorrhage or fresh infarction (including image in DWI, but no images in T2 and FLAIR) were observed under CT and MRI examination. Clinical manifestation and imageological examination had clearly confirmed as acute cerebral infarction⁸.

Inclusion Criteria

By reference to *China's Guidelines of Diagnosis and Treatment of Acute Ischemic Stroke 2010*:

Aged from 18 to 80 years old; Onset of illness within 4.5 hours; Signs of brain damages lasting for over one hour and in a serious condition; Intracranial hemorrhage is excluded after brain CT, and without early and large site cerebral infarction imaging changes; Patients or family members of patients signed an informed consent form.

Exclusion Criteria

Patients with previous history of intracranial hemorrhage, including suspected subarachnoid hemorrhage; with head trauma history in three months; with gastrointestinal hemorrhage or urinary system hemorrhage in three weeks; with major surgery in two weeks; with arteriopuncture on bleeding sites, which are not easy to press to stop for blood, in one week. Patients with cerebral infarction, or myocardial infarction within three months, but not including old small lacunar infarction accompanying without neurological signs. Patients with serious heart, liver, and renal insufficiency or serious diabetic patients. Patients with active bleeding or trauma (fracture) evidence after physical examination. Patients with oral administration of anticoagulant therapy, and INR > 1.5; with heparin therapy within 48 hours (APTT is beyond normal range). Patients whose blood platelet count < $100 \times 10^9/L$. Blood glucose < 2.7 mmol/L. Blood pressure: systolic pressure > 180 mmHg, or diastolic pressure > 100 mmHg. Gestation. Non-cooperation.

Thrombolysis Method

Calculate the dosage of alteplase by 0.9 mg/kg on the selected patients, of which 10% was injected intravenously in the first minute while the remaining 90% was dissolved into 250 ml nor-

mal saline and intravenously dipped in an hour. Reexamine brain MRI, MRA and make perfusion examination within 24 hours after thrombolysis (make CT examination on patients that cannot accept head nuclear magnetic imaging). After intracranial hemorrhage was excluded, patients were administered with oral aspirin 300 mg for once a day, and changed to 100 mg for once a day after being out of hospital^{9,10}.

Observation Index and Therapeutic Effect Evaluation

The NIHSS scoring before thrombolysis and the improved Rankin (MRS) scoring was observed after three months of follow-up to judge long term prognosis. A score between 0-1 under three months' MRS scoring was defined as favorable prognosis. A score between 2-5 or death was defined as poor prognosis¹¹⁻¹³. A head MRI was reexamined after thrombolysis and a CT scan was performed in the case of hemorrhage. The condition, which was confirmed by CT as hemorrhage and accompanied with neurological deterioration, was defined as symptomatic intracranial hemorrhage. The condition, which was confirmed by CT as hemorrhage but not accompanied with neurological deterioration, was defined as asymptomatic cerebral hemorrhage. The condition, which was confirmed by CT with non-hemorrhage, was defined as errhysis. Hemorrhage appeared in infarction were defined as infarction site errhysis, while in non-infarction site as non-infarction site errhysis¹⁴.

Correlation Factors that Influenced Treatment and Prognosis

Factors that might influence hemorrhagic transformation were selected. These included vascular wall¹⁵ (age, hypertension, diabetes mellitus, arteriosclerosis, stroke history, time window, tiny hemorrhage, vasculitis, trauma cause aortic dissection, myofiber hypoplasia of the progressive carotid artery, arterial aneurysm, vascular malformation, Moyamoya disease, worse collateral circulation, and other vascular endothelial injurious factors), blood components (oral administration of warfarin before thrombolysis, and aspirin after thrombolysis, fibrinogen, low platelet, protein S, protein C, early fibrinogen degradation coagulopathy, overdose of alteplase) and biochemical markers (matrix metalloproteinase, polycythemia, calcium binding protease increase). The patients' baseline NIHSS scoring were collected during the examination^{16,17}.

Statistical Analysis

The SPSS 21.0 statistical software (SPSS Inc., Chicago, IL, USA) was used to process the data and the *t* test for measurement data in single-factor analysis, and χ^2 test for enumeration data. A *p* < 0.05 value represented that the differences were significant. The statistical significant variables were selected from the single-factor analysis (*p* < 0.05) as an independent variable followed by a multi-factor unconditioned stepwise logistic regression analysis.

Results

A total of 1223 patients who were undergoing intravenous thrombolysis therapy of acute ischemic stroke in neurology department of Tianjin Huanhu Hospital from June 2012 to April 2014 were enrolled in the study. Amongst them were 898 males and 325 females, aged from 29-92 years old, with an average age of 62.2 ± 8.7 years old. Twenty-eight cases were between 18-39 years old (2.89%), 496 cases were between 40-59 years old (40.56%), 644 cases were between 60-79 years old (52.66%), and 55 cases were over 80 years old (4.50%). According to the NIHSS before thrombolysis (baseline NIHSS), 205 cases scored from 0 to 4 points (16.76%), 732 cases scored from 5 to 10 points (59.86%) and 286 cases scored over 11 points (23.39%).

The CT scan should be performed in the case of hemorrhage after an MRI reexamination of the head after thrombolysis. Forty-two cases were diagnosed with cerebral hemorrhage under MRI and 21 cases were diagnosed with cerebral hem-

Table I. Hemorrhage patients type after thrombolytic therapy.

Hemorrhage type	Number of people (case)	
Symptomatic cerebral hemorrhage	14	
Asymptomatic cerebral hemorrhage	7	
Errhysis	Errhysis in infarction site	19
	Errhysis in non-infarction site	2

orrhage under CT scan. In terms of hemorrhage type, 14 cases were diagnosed as symptomatic intracranial hemorrhage and seven cases as asymptomatic intracranial hemorrhage. In terms of errhysis site, 19 cases were infarction site errhysis and two cases were non-infarction site errhysis (Table I).

We analyzed the related risk factors in patients with hemorrhagic transformation. Amongst the patients with a history of hypertension, 10 cases were accompanied with symptomatic cerebral hemorrhage, four cases with asymptomatic cerebral hemorrhage and two cases with errhysis. Amongst the patients with a history of diabetes, six cases were accompanied with symptomatic cerebral hemorrhage, five cases with asymptomatic cerebral hemorrhage and 13 cases with errhysis. Amongst the patients with a history of stroke, four cases were accompanied with symptomatic cerebral hemorrhage, two cases with asymptomatic cerebral hemorrhage and six cases with errhysis (Table II).

Forty-two cases with non-hemorrhagic transformation from the patients under thrombolytic therapy were randomly drawn and compared for their history of hypertension, diabetes, and

Table II. Relationship types and risk factors in patients with hemorrhage after thrombolytic therapy.

	Symptomatic cerebral hemorrhage	Asymptomatic cerebral hemorrhage	Errhysis	<i>p</i>
Hypertension	10	4	15	< 0.05
Diabetes mellitus	6	5	13	< 0.05
History of stroke	4	2	6	< 0.05
Tiny hemorrhage	0	0	4	—
Vasculitis	0	2	1	—
Trauma caused aortic dissection	0	0	1	—
Hypoplasia of progressive carotid artery myofiber	0	0	1	—
Arterial aneurysm	4	3	6	> 0.05
Vascular malformation	0	0	2	—
Moyamoya disease	0	0	1	—
Worse collateral circulation	0	1	3	< 0.05
Other vascular endothelial injurious factors	1	2	5	< 0.05

stroke. The results showed that the history of hypertension, diabetes, and stroke were important factors that would affect hemorrhagic transformation (Table III).

Discussion

Amongst the enrolled 1223 cases with intravenous thrombolysis therapy of acute ischemic stroke, 42 cases suffered from hemorrhage after head MRI examination, and amongst them 21 cases were diagnosed with cerebral hemorrhage after CT scan while the others as errhysis¹⁸⁻²⁰. Hemorrhagic transformation after thrombolysis was a complicated but important pathophysiological process. It was an important bottleneck that could determine whether thrombolysis could be carried out smoothly or not^{21,22}.

Through the study analysis, we came to the conclusion that hemorrhagic transformation after thrombolysis is closely related with the vascular wall (age, hypertension, diabetes, arteriosclerosis, stroke history, time window, tiny hemorrhage, vasculitis, trauma cause aortic dissection, hypoplasia of progressive carotid artery myofiber, arterial aneurysm, vascular malformation, Moyamoya disease, worse collateral circulation, and other vascular endothelial injurious factors), blood components (oral administration of warfarin before thrombolysis, and aspirin after thrombolysis, fibrinogen, low platelets, protein S, protein C, early fibrinogen degradation coagulopathy, overdose of alteplase) and biochemical markers (matrix metalloproteinase, polycythemia, calcium binding protease elevation). They play an important role in hemorrhagic transformation after thrombolysis.

Vascular Wall

Hemorrhagic transformation after thrombolysis was the result of vascular wall damage. So, any factors that would damage the integrity of the vessel would also result in hemorrhagic transformation^{23,24}.

Age

Age has always been regarded as a dangerous factor that would affect hemorrhagic transformation after thrombolysis of acute ischemic stroke. The odds ratio would increase by 1.3 for every 10 years²⁵⁻²⁷. A higher risk of hemorrhage was related with high occurrence rate of microangiopathy, especially the aged patients with cerebral amyloid angiopathy and patients with leukoaraiosis²⁸. A 2013 AHA/ASA early treatment guidelines of acute ischemic stroke had proposed to take onset within 3 hours for patients aged ≥ 18 , and onset within 3-4.5 hours for patients aged > 80 as relative exclusion criteria.

Hypertension

Hypertension was the most common factor that would result in hemorrhagic transformation after thrombolysis of acute ischemic stroke. So strict control and monitor of blood pressure was necessary²⁹⁻³². While monitoring blood pressure, we paid attention to the low blood pressure caused by subclavian artery stenosis. We also detected the blood pressure of upper limbs and lower blood pressure on limbs on the relative broad side of subclavian artery, that is, on whichever side was higher³³. The 2013AHA/ASA early treatment guidelines of acute ischemic stroke had proposed to control the systolic pressure < 185 mmHg, and the diastolic pressure < 110 mmHg before thrombolytic therapy (Type I, level of evidence B).

Diabetes Mellitus

The risk of ICH would increase by 1.75 times as baseline plasma glucose rose by every 100 mg/dl. Hyperglycemia directly caused bad clinical results through aggravating acute brain damages^{34,35}. Patients, whose blood glucose exceeded 200mg/dl before treatment, would have an increasing risk of sICH³⁶. Hyperglycemia led to microangiopathy and blood brain barrier impairments, which would result in hemorrhagic transformation of cerebral infarction^{37,38}. The 2013 AHA/ASA early treatment guidelines of acute ischemic stroke had proposed to take continuous

Table III. Comparison of the relevant factors of hemorrhagic transformation after thrombolysis.

	Hemorrhagic transformation	Non-hemorrhagic transformation	χ^2	p
Hypertension	29	20	3.97	< 0.05
Diabetes mellitus	27	17	4.77	< 0.05
History of stroke	12	4	4.94	< 0.05

hyperglycemia (> 140 mg/dL) > 7.8 mmol/L in the first 24 hours after stroke as unfavorable outcome. It was quite reasonable to treat hyperglycemia, to control the blood glucose level within 140-180 mg/dL (7.8-10.3 mmol/L), and to monitor blood glucose level closely to avoid hypoglycemia (Type IIa, level of evidence C).

Arteriosclerosis

Cerebral arteriosclerosis reduced the vascular elasticity and increased vascular fragility. So it was easy to cause rupture hemorrhage³⁹.

History of Stroke

2013 AHA/ASA early treatment guidelines of acute ischemic stroke had proposed to take the onset of illness between 3-4.5 hours, along with history of diabetes and ischemic stroke, as relative exclusion criteria.

Time Window

After stroke occurred, nerve cytotoxic edema would appear, and the integrity of blood brain barrier would gradually be broken over time, which finally would result in hemorrhagic transformation⁴⁰.

Tiny Hemorrhage

Acute cerebral infarction patients with CMBs had a higher possibility of having hemorrhagic transformation than patients without CMBs after thrombolytic therapy or anticoagulant therapy⁴¹. Ischemic stroke patients, which had been found with tiny CMBs on MRI anticoagulant therapy before treatment, could continue to accept thrombolytic therapy safely. But additional CMBs might be the result of diffused hemorrhage⁴². Patients with a history of cerebral hemorrhage under CT examination shall be considered as a contraindication of thrombolysis⁴³.

Vasculitis

Vasculitis referred to inflammatory cell infiltration in and surrounding the vascular wall, being accompanied with blood vessel damages, including cellulose deposition, collagen denaturation, the endothelial cells and the muscle cell necrosis. Vasculitis would reduce vascular elasticity and produce hemorrhagic transformation after thrombolytic therapy⁴⁴.

Arterial Aneurysm

The size of arterial aneurysm was an important factor that would influence aneurysm rupture, but danger threshold of aneurysm rupture was not

certain⁴⁵. International multi-center defined 10 mm arterial aneurysm as rupture and bleeding threshold. Fast flow velocity in the tumor body, small impacted area, and strong wall shear stress were all closely related with aneurysm rupture.

Other factors that would influence vascular wall included trauma caused aortic dissection, hypoplasia of progressive carotid artery myofiber, vascular malformation, Moyamoya disease, worse collateral circulation, and other vascular endothelial injurious factors (blood ammonia, creatinine, and homocysteine elevation)⁴⁶.

Blood Components Factors

Oral Administration of Warfarin Before Thrombolysis

The 2013 AHA/ASA early treatment guidelines of acute ischemic stroke had proposed an exclusion criteria for onset within three hours: oral administration of anticoagulation INR >1.5 or PT >15 seconds; the exclusion criteria for onset within 3-4.5 hours: oral administration of anticoagulation, whatever the INR value.

Application of Aspirin After Thrombolysis

Reexamine the CT or MRI 24 hours later after the application of aspirin intravenously and before the application of anticoagulation or antiplatelet drugs. Aspirin (or other antiplatelet drugs) was not recommended to be used as adjuvant therapy within 24 hours after intravenous thrombolytic therapy (Type III, the level of evidence C).

Protein S and Protein C

Activated protein could limit the combination of factor Xa and platelet, strengthen the dissolution of protein, and inactivate coagulation factors V and VIII. Protein S could activate protein C. As protein S increased and protein C became activated, hemorrhagic transformation would also increase⁴⁷.

Early Fibrinogen Degradation Coagulopathy

In thrombolytic therapy, the extrinsic plasminogen activator could accelerate the transformation of plasminogen into plasmin, thus realizing thrombolysis. Early fibrinogen degradation coagulopathy would consume a large amount of fibrinogen and result in the shortage of fibrinogen, thus leading to hemorrhagic transformation during the early period after thrombolysis⁴⁸.

Overdose of Alteplase

Overweight patients always needed a large amount, so it resulted in an overdose of alteplase. The higher the thrombolytic drug dose, the higher the incidence rate of hemorrhagic transformation. Therefore the dose of re-PA is limited to 0.9 mg/kg weight at present, with a maximum of 90 mg⁴⁹.

Biochemical Markers

Matrix metalloproteinase (MMP) was involved in hemorrhagic transformation and their activated part resulted in blood brain barrier (BBB) damages⁵⁰. The activation of MMP-9 was related with permeability increase of BBB, which finally resulted in edema and hemorrhagic transformation.

Conclusions

Aside from polycythemia, the increase of calcium binding protease and other biochemical markers would also lead to hemorrhagic transformation⁵¹. As well, the time or pathophysiological window, the assessment of hemorrhagic transformation after intravenous thrombolysis therapy on acute ischemic stroke patients should also include a comprehensive analysis of blood vessel, blood components and biochemical markers. As our intravenous thrombolysis studies go further and deeper, we will discover more other factors related with hemorrhagic transformation.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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