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Study on the effect of urinary kallidinogenase after thrombolytic treatment for acute cerebral infarction

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Abstract. – OBJECTIVE: To evaluate the safety and efficacy of urinary kallidinogenase for recombinant tissue-type plasminogen activator (rt-PA) intravenous thrombolytic treatment in patients with acute cerebral infarction.

PATIENTS AND METHODS: All 200 patients with acute cerebral infarction were randomized 1:1 into an experimental group (100 cases) and a control group (100 cases). Patients in the control groupwere administrated rt-PA (0/9 mg/kg) while patients in the experimental group were given urinary kallidinogenase by intravenous drip (0.15 PNAU/d, for 7 days) after rt-PA intravenous thrombolytic treatment (0.9 mg/kg). The main evaluation index was NIHSS and BI.

RESULTS: Compared to the control group, the NIHSS scores were significantly lower 7 and 90 days after thrombolytic therapy (t = 2.391, 2.714; $p < 0.05$). BI scores were obviously higher at 90 days after thrombolytic therapy in the experimental group (t = 2.675, $p < 0.05$).

CONCLUSIONS: Urinary kallidinogenase may improve the treatment effect for rt-PA intravenous thrombolytic treatment in patients with acute cerebral infraction.

Key Words:
Tissue plasminogen activator, Human urinary kallikrein, Acute cerebral infarction.

Introduction

The most effective treatment of acute cerebral infarction is thrombolytic therapy[1,2]. Recombinant tissue plasminogen activator, rt-PA was approved for thrombolytic therapy by the US Food and Drug Administration in 1996. Human urinary kallikrein, namely kallikrein, is a glycoprotein extracted from urine[3]. Clinical studies have confirmed that it can activate its kallikrein-kinin system, expand arterioles of the cerebral ischemia area and aggregate anti-platelet. Currently, clinical studies about the combination of thrombolytic and kallikrein are rare[4]. The purpose of this study is to observe the efficacy of thrombolytic and kallikrein on acute cerebral infarction.

Patients and Methods

Two hundred patients receiving thrombolytic therapy between June 2012 and January 2014 were selected for this study. Of all the patients, 109 are men and 91 women with an age between 35 and 80 years old and an average age of 63 (5 ± 8.7 years old). The thrombolysis inclusion criteria are: (1) Age not more than 80; (2) Diagnosed as ACI and the NIHSS is between 4 and 25; (3) No intracranial hemorrhage and obvious low density shadow found by head CT scan; (4) Time of onset is not more than four and half hours; (5) Thrombolytic informed consent signed by family members or patients. Exclusion criteria are: (1) History of intracranial hemorrhage including suspicious subarachnoid hemorrhage, head trauma in the last three months, bleeding in gastrointestinal or urinary system in the last three weeks, major surgery in the last two weeks and arterial puncture of oppression-forbidden area in the last week; (2) History of cerebral or myocardial infarction in the last three weeks with exception of patients with no neurological function signs left in old locule gaps; (3) Severe heart, kidney, liver dysfunction or severe diabetes patients; (4) Active bleeding or trauma found at examination; (5) Oral anticoagulation and the INR is over 1.5, heparin treatment within 48 hours (aPTT time outside the normal range); (6) Blood platelets less than 100×109/L, blood sugar less than 2.7 mmol/L; (7) Blood pressure:

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Table I. The baseline data of two groups.

	Experimental group	Control group
Age	58.8 ± 10.6	61.2 ± 9.7
Gender (Male/Female)	54/46	55/45
ADL Score	46.3 ± 16.2	52.9 ± 17.6
NHISS Score	13.8 ± 5.9	12.7 ± 6.2
History of high blood pressure (%)	68 (68)	72 (72)
History of coronary heart disease (%)	35 (35)	32 (32)
History of diabetes mellitus (%)	39 (39)	42 (42)

systolic blood pressure over 180 mmHg and diastolic blood pressure over 100 mmHg; (8) Gestation; (9) Non-cooperation.

Patients and Methods

The patients included in the treatment program were divided into the control group and the experimental group. All patients received rt-PA thrombolytic therapy with 0.9 mg/kg (total amount less than 90 mg), 10% by intravenous injection in one minute and 90% by intravenous drip in 60 minutes. The experimental group received kallikrein (0.15 PNA/d, continuous for 7 d) after thrombolytic therapy. It was forbidden to use angiotensin-converting enzyme inhibitors in the treatment. The control group received blood platelets treatment after 24 hours with aspirin of 300 mg QD. At the same time, hypotensive, hypoglycemic, lipids-lowering, anti-atherosclerosis, and plaque stability treatments were administered for complications like diabetes mellitus, hypertension, carotid artery plaque, and hyperlipidemia.

The NIHSS of the National Institutes of Health was used to assess the neurological functions of patients, seven days before treatment, and 90 days after treatment. The BI index was used to assess the daily living ability of patients 90 days after treatment.

Statistical Analysis

The SPSS for Windows 16.0 statistical package (SPSS Inc., Chicago, IL, USA) was used to process data. The measurement data was presented as z ± s and analyzed with *t*-test. Count data were tested with χ^2. $p <$ was considered statistically significant.

Results

The baseline data of the two groups were as follows: there was no evident difference (all over 0.05) in age, gender, and daily living ability, HISS of the National Institutes of Health, history of high blood pressure, coronary heart disease and diabetes scores (Table I).

Comparison of NIHSS before and after treatment between two groups. The NIHSS score has obviously improved (average p less than 0.05) seven days and 90 days after treatment respectively. The experimental group is better than the control group (p less than 0.05) (Table II).

Comparison of BI before and after treatment between two groups. The BI score has improved (average p less than 0.05) 90 days after treatment. The experimental group is better than the control group (p less than 0.05). (Table III).

Discussion

The treatment of acute cerebral infarction has always been a hot research topic, and thrombolytic therapy is one of the few Class I recom-

Table II. Different time NHISS score with two groups of patients.

Group	Number	NHISS Score before Thrombolysis	NHISS Score Seven Days Later	NHISS Score 90 Days Later
Experimental group	100	13.8 ± 5.9	4.2 ± 3.8	1.2 ± 2.6
Control group	100	12.7 ± 6.2	6.9 ± 5.9	3.9 ± 5.7
Value of *t*		0.952	2.391	2.714
Value of *p*		0.379	0.045	0.041

Table III. Different time BI score with two groups of patients.

Group	Number	BI Score before Thrombolysis	BI Score 90 Days Later
Experimental group	100	35.7 ± 12.9	89.2 ± 21.6
Control group	100	33.7 ± 16.2	63.9 ± 25.7
Value of *t*		0.832	2.675
Value of *p*		0.787	0.012

mendations in the guideline with the evidence A level. Back in 1995, the NINDS proved the effectiveness of acute cerebral infarction in the rt-PA intravenous thrombolytic therapy time window at a large scale clinical experiment[5-8]. The purpose of thrombolytic therapy is to dredge vascular occlusion and restore blood flow in the infarct zone. However, this can bring about continuous bleeding and reperfusion injury[9-14].

Urinary kallikrein is tissue kallikrein extracted from the urine. Studies have shown that it can activate kallikrein-kinin system[15,16], transfer kininogen hydrolysis into kinin and kallidin and combine with BI receptor produced under induction of ischemic brain tissue to release nitric oxide and relax vascular smooth muscle[17,18]. Thus, it can expand blood vessels in the ischemic area, improve cerebral blood supply of penumbra and restore the neurological deficit as soon as possible. Furthermore, urinary kallikrein can advance growth of new blood vessels[19-21].

Ling et al found that, urinary kallikrein can induce nerves endogenous around the focus of infarct of MCAO-handled mice[22-24]. Recently, their studies have shown that urinary kallikrein can activate ERK1/2 signal pathway of cultured neurons and enhance neurons' ability to resist ischemia-reperfusion and the ischemic acidosis[25,26].

Conclusions

The results show that, the NIHSS scores of the experimental group are all lower than those of the controlgroup at seven days and 90 days after thrombolytic therapy and the BI scores are higher than those of the control group. They also show that the use of rt-PA intravenous thrombolysis with urinary kallikrein on acute cerebral infarction can improve neurological deficit significantly, long-term prognosis and quality of life. This may be related to biological effects of inhibition of urinary kallikrein on ischemia-reperfusion inflammation, expansion of the tiny blood vessels and improvement of circulation and inhibition of apoptosis[27-30].

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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