Efficacy of different doses of alteplase thrombolysis on acute ischemic stroke in patients

Hongying Xu*
Department of Critical Care Medicine, Affiliated Hospital of Jining Medical University, Jining, China

Abstract: Atyplase is a kind of thrombolytic drug with strong fibrin specificity. It can promote the synthesis of fibrinolytic enzymes by combining fibrin and plasminogen in thrombus, and then dissolve thrombus. Ateplase intravenous thrombolysis is the only effective method for stroke treatment proved by evidence-based medicine. The aim of this study was to observe the effect of different doses of ateplase on acute ischemic stroke. They were randomly divided into control group (n=43) and observation group (n=43). The patients in the control group were treated with low-dose alteplase, while those in the observation group were treated with standard-dose alteplase. The control group was treated with 0.6 mg/kg ateplase intravenous thrombolysis, and the observation group was treated with 0.9mg/kg ateplase. The GCS scores on the 1 day was 14.06±1.57 in the control group after treatment, and 13.84±2.48 in the observation group. The NIHSS score was 4.59±1.12 in the control group, and 7.13±1.05 in the observation group. Intravenous thrombolytic therapy with intravenous thrombolytic therapy is effective and safe in the treatment of acute ischemic stroke. At the same time, there were no persistent adverse reactions after treatment, mainly in gingival bleeding, epistaxis, intracranial hemorrhage, gastrointestinal bleeding, and hematuria and so on. The results showed that different doses of alteplase could improve neurological function and living ability of patients. Future studies need to broaden the sample size to study the safety of low and standard doses of alteplase in patients with acute cerebral infarction

Keywords: Alteplase, ischemic stroke, neurological function, thrombolytic drugs.

INTRODUCTION

Ischemic stroke is mainly due to the occlusion of arteries and blood vessels supplying the corresponding brain tissue, resulting in ischemic and hypoxic injury of local brain tissue (Anderson *et al.,* 2016; Mu *et al.,* 2018). After ischemic stroke, the intracranial collateral circulation vascular network can provide compensatory blood flow to ischemic brain tissue. Ateplase, which has a good affinity for fibrin in thrombosis, it has a half-life of only 5 minutes and a high selectivity for fibrin (Benson *et al.,* 2017; Gong *et al.,* 2018). It is the only drug approved by the FDA for thrombolytic therapy of ischemic stroke in the United States and is pre-empted (Bergmann *et al.,* 2016). Due to the small scale of the study on the ideal dosage of ateplase, there is still a great deal of controversy about the standard dosage of ateplase and some people believe that the Asian population is more prone to bleeding when using ateplase (Chen *et al.,*2009; Rey *et al.,*2018).

Arteplase can dredge the cerebral vessels contracted by ischemia again in the acute stage, rescue the brain cells in the ischemic penumbra as soon as possible, and alleviate the neurological impairment of patients (Ahmed *et al.,* 2013; Ramos *et al.,* 2018). Arteplase is a recombinant tissue plasminogen activator (rtPA). A strong fibrin-specific thrombolytic agent can bind to cellulose in thrombus, and has a high affinity to the bound plasminogen. It can promote the conversion of plasminogen to plasmin, thus promoting thrombolysis Ghoneum *et al.,* 2015). In theory, rtPA should have stronger thrombolytic effect than streptokinase (SK) and urokinase (UK) and bleeding. This has been confirmed by animal experiments. However, bleeding has also been reported in clinical practice. Nevertheless, randomized trials of multiple large samples have shown the efficacy and safety of rtPA in thrombolytic therapy for acute ischemic stroke. rtPA is currently the only way through the Food and Drug Administration of the United States (FDA). Thrombolytic drugs approved for acute ischemic stroke have a very short half-life (only 3-6 minutes), a certain rate of vascular re-closure and need to be continuously administered, and their sources are limited and the price is high, which limits their clinical application to a certain extent. troke is the main cause of death in China (Dindo *et al.,* 2004; Bernuy *et al.,* 2018). Thrombolytic therapy is considered to be the most effective method to improve the prognosis of acute cerebral infarction, but the narrow time window limits the treatment opportunities of many patients (Goyal *et al.,* 2016; Campuzano *et al.,* 2018). Ateplase intravenous thrombolysis is the only evidence-based medicine proven effective method for stroke treatment, and recommended by multi-national guidelines, with the clinical application of Ateplase, the mortality and disability rate of acute ischemic stroke significantly reduced (Jiahua *et al.,* 2011). Ateplase has a strong affinity for plasminogen in thrombosis and has a specific local thrombolytic effect, but a weak affinity for plasminogen in blood circulation,

**Corresponding author:* e-mail: zzyxjyfy@163.com

systemic fibrinolysis is not obvious (Hlavica *et al.*, 2015). A number of large-scale clinical studies have demonstrated that intravenous thrombolysis with ateplase is safe in the treatment of acute ischemic stroke (Behrouz, 2014). Atyplase is the first choice drug for clinical treatment of acute ischemic stroke. It is a kind of thrombolytic drug with strong fibrin specificity. It can promote the synthesis of fibrinolytic enzyme by combining fibrin and plasminogen in thrombus, then dissolve thrombus, dredge cerebral vasoconstriction again, save the brain cells that are dying and improve it. All are effective, but because of practical clinical problems and the standard limitations of treatment time windows, as well as the lack of public and professional education on stroke as a treatable emergency event, only less than 2% of patients can receive emergency thrombolytic therapy with ateplase (Inzucchi *et al.*, 2015). Although ateplase has been approved for intravenous thrombolysis, there is no large-scale clinical controlled study in China to confirm the safety and effectiveness of the treatment (Jean *et al.*, 2017). The aim of this study was to observe the effect of different doses of apipsin on acute ischemic stroke.

MATERIALS AND METHODS

Case selection and exclusion criteria

Selection criteria of acute ischemic stroke patients admitted to our hospital from January 2016 to December 2017 were as follows: (1) age 18-75 years old, onset time within 4.5 hours, except cerebral hemorrhage and obvious low density changes by cranial CT examination; (2) signs of brain function damage lasting more than 1 hour; (3) Neurological symptoms and signs of acute cerebral infarction were not relieved; (4) There was no obvious disturbance of consciousness, and the blood pressure was less than 180 /100 mm Hg. All patients were approved by ethics committee of our hospital, ethical approval number as AHJMU13PD2015 and all patients signed on the informed consent.

Exclusion criteria

Exclusion marking reference to Chinese guidelines for diagnosis and treatment of acute ischemic stroke 2018: (1) The clinical symptoms improved significantly before treatment; (2) History of intracranial hemorrhage, 48 hours of heparin or anticoagulant use, 7 days of arterial puncture, 14 days of major surgery, 30 days of gastrointestinal bleeding and urinary tract bleeding, 3 months of head trauma and cerebral infarction, old lacunar infarction left neurological signs; (3) Prothrombin time (PT) <15 s, activated partial thromboplastic time (APTT) <40 s, international normalized ratio (INR) 1.5, and platelet count $<10*10^9$/L are receiving anticoagulant therapy; (4) Suspected subarachnoid hemorrhage, intracranial aneurysm, intracranial tumor, arteriovenous malformation; (5) There are serious heart, liver and kidney dysfunction, pregnancy; (6)Hypertension or hypotension (systolic blood pressure <100 mm Hg), suspected to be caused by hemodynamic mechanisms of cerebral infarction.

Grouping

A total of 86 patients with acute cerebral infarction were randomly divided into two groups: low-dose group (0.6 mg/kg) of 43 cases, 25 males and 18 females; age (41.2±10.7) years; Glasgow coma scale (GCS) at admission (13.56±1.28). The National Institutes of Health of Stroke Neurological Defects Scale (NIHSS) score was 8.46±6.13. The standard dose group (0.9 mg/kg) consisted of 43 patients, 22 males and 21 females, aged 46.57±12.3 years, GCS score at admission (16.74±2.04) and NIHSS score (8.91 6.54). No difference in age, sex, starting time of treatment, NIHSS score and GCS before treatment ($P > 0.05$).

Therapeutic method

After admission, according to the Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke, a green rescue channel was established for patients suspected of acute ischemic stroke. The cranial CT, electrocardiogram, blood coagulation, blood biochemistry and blood routine tests were performed in emergency to quickly establish a venous channel for the patients. Use of drugs refers to Ringleb (2016) method, acute ischemic stroke, within 3 hours of onset, using ateplase, the recommended dose is 0.9mg/kg body weight. Some Chinese studies show that low-dose ateplase drugs have the same effect on patients (Zhu *et al.*, 2015). In low dose group, the dosage of atenoprlase was 0.6mg/kg, the maximum dosage was 60mg, the first dose was 15% in 1 minute, and the remainder was maintained for 1 hour. Standard dosage group: Ateplase dosage was 0.9mg/kg, the maximum dosage was 90 mg, the first dose was 10% in 1 minute intravenous injection, the remaining volume maintained 1 hour intravenous pump. After 24 hours, no bleeding was confirmed by CT scan. All patients were treated with 100 mg aspirin enteric-coated tablets orally for 1 day.

Observation index

The NIHSS score and GCS score were compared between the two groups before treatment and 1 and 5 days after treatment; the improved Rankin (MRS) score was compared between the two groups before treatment and 1, 4, 8 weeks after treatment; and the total effective rate was compared between the two groups after treatment. Before and after treatment, patients were evaluated by the same professional physician to reduce the difference of data. The assessor did not participate in the treatment of patients.

Standard curative effect

NIHSS includes visual field, consciousness level, upper limb movement, gaze, lower limb movement and so on. The NIHSS score is 0-45. The higher the score, the more

Table 1: Comparison of GCS scores before and after treatment

Group	cases	Before treatment	1 days after treatment	5 days after treatment
Low dose group	43	13.25±1.28	14.06±1.57	14.21±1.64
Standard dose group	43	13.57±1.05	13.84±2.48	13.96±2.61

Table 2: NIHSS before and after treatment

Group	cases	Before treatment	1 days after treatment	5 days after treatment
Low dose group	43	8.75±2.41	4.59±1.12	5.64±2.17
Standard dose group	43	8.31±2.76	7.13±1.05	7.02±2.64

Table 3: Comparison of MRS scores

Group	cases	Before treatment	1 weeks after treatment	4 weeks after treatment	8 weeks after treatment
Low dose group	43	3.12±1.57	2.56±1.28	1.75±0.94	1.15±0.73
Standard dose group	43	2.89±1.42	2.61±1.74	2.25±1.63	1.72±1.14

Table 4: Comparison of curative effect of patients

Group	cases	recovery	Significant effect	Partial validity	invalid	Total effective rate
Low dose group	43	11	13	17	2	95.34
Standard dose group	43	8	9	22	4	90.69

Table 5: Adverse reaction

Group	cases	Gingival bleeding	Epistaxis	intracranial hemorrhage	Gastrointestinal bleeding	hematuria
Low dose group	43	6	9	3	5	1
Standard dose group	43	7	4	2	4	1

serious the neurological deficit is. The content of mRS assessment includes self-care ability, disability and so on. The mRS score is 0-6. The lower the score, the better the recovery of disability. Invalidity: NIHSS score decreased by less than 17%; improvement: NIHSS score decreased by 18%-45%; marked effect: patients NIHSS score decreased by 46%-90%; recovery: NIHSS score decreased by 91%-100%. Total effective = improvement + marked effect + recovery.

STATISTICAL ANALYSIS

SPSS19.0 statistical software was used to process the data. x2 test was used for counting data (%) and t test was used for measuring data (+s). $P<0.05$ was statistically significant.

RESULTS

Comparison of two groups of GCS

The GCS of 1 day and 5 days after treatment in the two groups were higher than that before treatment, as shown in table 1. Relevant data showed that the incidence of acute ischemic stroke accounted for 3/4 of stroke, and its mortality rate was high, which seriously threatened the life safety of patients. Therefore, it is of great significance to take active and effective prevention and treatment measures for patients with acute ischemic stroke, among which early opening of occluded blood vessels and restoring blood flow are the key to the treatment of acute ischemic stroke.

Comparison of two groups of NIHSS scores

Ateplase can directly activate plasminogen into plasmin, which is suitable for intravenous thrombolysis. When injected intravenously, fibrinogen is relatively inactive in the circulatory system; once it binds to fibrin, it is activated, which will induce fibrinogen to be converted into fibrinolytic enzyme, and fibrinolytic enzyme can degrade fibrin and dissolve blood clots (table 2).

Comparison of two groups of MRS scores

The MRS scores of the two groups at 4 and 8 weeks as shown in table 3. The effective rate as shown in table 4. The scores of mRS were lower than those of the control group and the good rate of recanalization of occluded vessels was higher than that of the control group. The results showed that standard dose of ateplase could effectively improve the degree of neurological deficit, improve the living ability of patients, improve the condition of cerebral artery blood supply and then facilitate recanalization of occluded vessels in patients with acute ischemic stroke.

Adverse reaction results

There were no serious adverse reactions in the two groups, 6 cases of gingival bleeding, 9 cases of epistaxis, 3 cases of intracranial bleeding, 5 cases of gastrointestinal

bleeding and 1 case of hematuria in the low dose group, 7 cases of gingival bleeding, 4 cases of epistaxis, 2 cases of intracranial bleeding, 4 cases of gastrointestinal bleeding and 1 case of hematuria in the standard dose group.

DISCUSSION

Stroke is a common clinical disease caused by many factors, such as diet, heredity, emotion and so on, which leads to cerebral vascular stenosis and occlusion, and then leads to insufficient blood supply to the brain (Zhu *et al.*, 2015). The patients will leave different degrees of sequelae, such as hemiplegia, mouth and eye deviation, language dysfunction, which seriously affects the quality of life of patients and increases their home. Ateplase can directly activate plasminogen into plasmin, which is suitable for intravenous thrombolysis after acute myocardial infarction, acute massive pulmonary embolism and acute ischemic stroke (Marshall *et al.*, 2015). When injected intravenously, fibrinogen is relatively inactive in the circulatory system; once it binds to fibrin, it is activated, which will induce fibrinogen to be converted into fibrinolytic enzyme. Acute cerebral infarction lesions consist of central necrosis area and its surrounding ischemic penumbra (Kai *et al.*, 2015). The central necrosis area is irreversible necrosis 10 minutes after vascular occlusion, while the ischemic penumbra has less infarction in a certain period of time because of the high regional cerebral blood flow (Kargulewicz *et al.*, 2016). Therefore, the reversibility of ischemic penumbra injury is the pathological basis of emergency thrombolysis in patients with ischemic stroke. Thrombolytic therapy can make the occluded blood vessel open quickly, reperfusion of the damaged area quickly, and then rescue the nerve cells in reversible injury state to the greatest extent, so that nerve function can be restored quickly (Logallo *et al.*, 2017). Ateplase is a second-generation thrombolytic drug with a half-life of 5 minutes. It can selectively bind to fibrin on the surface of thrombus. Ateplase can transform effective plasminogen into fibrinolytic enzyme locally to achieve thrombolysis (Marshall, 2015). Thrombolytic action is limited to the thrombosis site and has stronger specificity. However, the price of the drug is limited and its clinical application is limited (Powers *et al.*, 2018). NIHSS and mRS scores of routine dose group were lower than those of low dose group 24 hours and 3 months after treatment (Roman *et al.*, 2011). However, it is necessary to master the time window of thrombolysis to maximize the improvement of blood flow in infarcted areas, restore blood supply to the ischemic penumbra, and provide better treatment opportunities for more patients (Dindo *et al.*, 2004).

The greatest adverse reaction of intravenous thrombolysis in patients with acute ischemic stroke is secondary intracranial hemorrhage. Traditional thrombolytic agents have a wide range of action and poor specificity (Ringleb *et al.*, 2016). Fibrinogen in plasma is activated while fibrinolysis occurs, which can easily lead to systemic hemorrhage. R-PA has a strong affinity for plasminogen, a specific local thrombolysis, can effectively avoid non-selective fibrinolysis, a small affinity for plasminogen in the blood circulation, and has no obvious effect on systemic fibrinolysis, so the systemic effect of the components of the whole coagulation system is slight, rarely causing bleeding. In this study, 5 patients had cerebral hemorrhage after thrombolysis (Benson *et al.*,2017). The mechanism of cerebral hemorrhage may be related to secondary fibrinolysis and coagulation disorders after ischemia, reperfusion injury and poor blood pressure control (Steiner, 2012). However, the sample size of this study is small and needs to be further increased. According to the observation of intravenous thrombolytic effect in 4.5 hours (Whiteley *et al.*, 2016).

The results of this study showed that there was no significant difference in NIHSS scores between the two groups before treatment. After treatment, the NIHSS scores of the two groups were improved, but the NIHSS scores of the low dose group were better than those of the conventional dose group (Marshall, 2015). Monthly NIHSS score and mRS score were lower than those of low dose group (Xuexiu *et al.*, 2015). There was no significant difference in the total effective rate between the low dose group and the conventional dose group ($P > 0.05$). To sum up, routine dose of intravenous thrombolysis with ateplase can improve the neurological function and living ability of patients with acute ischemic stroke, and contribute to the recovery of prognosis.

CONCLUSION

To sum up, intravenous thrombolysis with ateplase is effective and safe in the treatment of acute ischemic stroke. For future research, we need to expand the sample size, on the one hand, to study the safety of patients with acute cerebral infarction receiving low-dose and standard-dose alteplase under the influence of different risk factors, on the other hand, to make the efficacy of low-dose alteplase in the treatment of acute cerebral infarction more convincing.

REFERENCES

Anderson CS, Robinson T and Lindley RI (2016). Low-dose versus standard-dose intravenous alteplase in acute ischemic stroke. *N. Engl. J. Med.*, **374**: 2313-2323.

Ahmed N, Kellert L and Lees KR (2013). Results of intravenous thrombolysis within 4.5 to 6 hours and updated results within 3 to 4.5 hours of onset of acute ischemic stroke recorded in the Safe Implementation of Treatment in Stroke International Stroke Thrombolysis Register (SITS-ISTR): An observational study. *JAMA Neurol.*, **70**(7): 837-884.

Bernuy N, Elena V and Maria S (2018). Influence of the consumption of quinoa (*Chenopodium quinoa* Willd.) on the accumulation of adipose tissue and antioxidant activity in tissues of obese rats, *Arch. Latin. Nutr.,* **68**(2): 111-121.

Benson H and Raghavan R (2017). Mitochondrial function in hypoxic ischemic injury and influence of aging. *Progre. Neuro.,* **157**: 92-116.

Bergmann A, Thuler LC, Moore MA and Nam BH (2016). Construction of modern logistics distribution center. *Logi. Tech.*, **2**(4): 203-214.

Behrouz R (2014). Intravenous tenecteplase in acute ischemic stroke: An updated review. *J. Neurol.,* **261**(6):1069-1072.

Chen J, Liu S, Pan J, Zheng X, Zhu K, Zhu J, Xiao J and Ying M (2009). Simulation model and optimization of medical delivery system. *Comp. Eng.*, **36**(3): 80-486.

Campuzano B, Miguel A, Rodon L and Vera L (2018).Effect of consumption of *Carica papaya* pulp on glycaemia and weight of normo and alloxan induced hyperglycemic mice, *Arch. Latin.Nutr.*, **8**(2): 132-140.

Dindo D, Demartines N and Clavien PA (2004). Marketing strategy and mode selection of pharmaceutical enterprises. *Disc. Mod. Eco.*, **240**(2): 205-213.

Goyal M and Menon B (2016). Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. *Lancet*, **387**(10029): 1723-1731.

Ghoneum M, Felo N, Nwaogu OM, Fayanju IY, Jeffe JA and Margenthaler DB (2015). Logistics help pharmaceutical distribution competition. *Log. Tech. App.*, **1**(2): 73-82.

Gong Z, Li X and Liu J (2018). Ibuprofen Drug Management and Centralization Strategy of Pharmaceutical Retail Enterprises, *Bole. Mala. Sal. Amb.*, **58**(3): 81-94.

Hlavica M, Diepers M and Garcia-Esperon C (2015). Pharmacological recanalization therapy in acute ischemic stroke - evolution, current state and perspectives of intravenous and intra-arterial thrombolysis. *J. Neuroradiol.,* **42**(1): 30-46.

Inzucchi S, Zinman B, Wanner B and Ferrari R (2015). SGLT-2 inhibitors and cardiovascular risk: Proposed pathways and review of ongoing outcome trials. *Diab. Vasc. Dis. Res*., **12**(2): 90-100.

Jiahua Y, Hwa L, Sang L, Hee Y and Woo S (2011). Aggravation of post-ischemic liver injury by overexpression of A20: An NF-κB suppressor. *J. Hepat.,* **55**(2): 328-336.

Jean Y, John X, Stephen E and Claude G (2017). Canagliflozin in Conjunction With Sulfonylurea Maintains Glycemic Control and Weight Loss Over 52 Weeks: A Randomized, Controlled Trial in Patients With Type 2 Diabetes Mellitus. *Clini. Therap.,* **39**(11): 2230-2242.

Kai S, Jingyu F and Jingyan H (2015). Ameliorating effects of traditional Chinese medicine preparation, Chinese materia medica and active compounds on ischemia/reperfusion-induced cerebral microcirculatory disturbances and neuron damage. *Acta. Pharm. Sinic. B.*, **5**(1): 8-24.

Kargulewicz A, Szulinska M, Kujawska-Luczak E, Swora CK and Musialik M (2016). Improvement of serum adiponectin and leptin concentrations: effects of a low-calorie or isocaloric diet combined with metformin or orlistat- a prospective randomized open-label trial. *Eur. Rev. Med. Pharmacol. Sci.*, **20**(18): 3868-3876.

Logallo N, Novotny V and Assmus J (2017). Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): A phase 3, randomised, open-label, blinded endpoint trial. *Lanc. Neur.,* **16**(10): 781-788.

Mu Y and Gao J (2018). Effects of Rosiglitazone Therapy and Exercise Training on Glycolipid Metabolism in Patients with T2DM, *Bole. Mala. Sal. Amb.,* **58**(3): 75-80.

Marshall RS (2015). Progress in intravenous thrombolytic therapy for acute stroke. *JAMA Neuro.,* **72**(8): 928-934.

Powers WJ, Rabinstein AA and Ackerson T (2018). 2018 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*, **49**(3): 46-e99.

Ramos-Jimenez A, Hernandez T and Rosa P (2018). Anthropometric equations for calculating body fat in young adults, *Arch. Latin. Nutr.,* **68**(2): 111-121.

Roman S, Viktor R, Hanna S, Yury M, Tamara M and Jerry L (2011). Baicalein alleviates diabetic peripheral neuropathy through inhibition of oxidative nitrosative stress and p38 MAPK activation. *Experi. Neur.,* **230**(1): 106-113.

Rey E and Ladino W (2018).Treatment for Malaria by using Primaquine therapy, *Bole. Mala. Sal. Amb.*, **58**(2): 2-4.

Ringleb P and Hamann G (2016). Akuttherapie des ischämischen Schlaganfalls-Rekanalisierende Therapien. *Akt. Neurol.,* **43**(2): 82-91.

Steiner T (2012). Neue direkte orale Antiokoagulantien-was im Notfall zu beachten ist. *Dtsc. Arzte.*, **109**(39): 1928-1930.

Whiteley WN, Emberson J, Lees KR (2016). Risk of intracerebral haemorrhage with alteplase after acute ischaemic stroke: A secondary analysis of an individual patient data meta-analysis. *Lanc. Neur.,* **15**(9): 925-933.

Xuexiu H, Zhengkai W, Ershun Z, Libin C, Jinhua K and Jingjing W (2015). Baicalein attenuates inflammatory responses by suppressing TLR4 mediated NF-κB and MAPK signaling pathways in LPS-induced mastitis in mice. *Intern. Immuno.*, **28**(1): 470-476.

Zhu Y and Chen W (2015). Chinese herbal medicine logistics company access standards. *Med. Wor.*, **20**(6): 1585-1591.