Efficacy of fingolimod combined with alteplase in acute ischemic stroke and rehabilitation nursing

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Abstract: This paper aims to observe and analyze the safety and clinical efficacy of Fingolimod combined with alteplase intravenous thrombolysis in the treatment of acute ischemic stroke. 90 patients with acute ischemic stroke were randomly divided into two groups. 45 patients in the control group were given alteplase intravenous thrombolysis for injection. 45 cases in the trial group were treated with Fingolimod combined with alteplase. There was no significant difference in NIHSS score, mRS score and BI index between the two groups 14 days after treatment, but 90 days after treatment, NIHSS score and mRS score of the experimental group were significantly lower than that of the control group, and BI index was significantly higher ($P<0.05$). 24 hours after oral administration of Fingolimod (0.5 mg), the circulating blood CD4 + T, CD8 + T, CD19 + B and CD56 + natural killer cells of the patients in the combined treatment group decreased steadily to varying degrees. The results confirm the pharmacological effect of Fingolimod: it changes lymphocyte migration, promotes lymphocyte to enter lymphoid tissue, prevents lymphocyte from leaving lymphoid tissue to enter the peripheral circulation, and thus prevents these immune cells from infiltrating the central nervous system. The results showed that Fingolimod combined with alteplase intravenous thrombolysis is safe for patients with acute ischemic stroke.

Keywords: Stroke, intravenous thrombolysis, fingolimod, alteplase, atherosclerosis.

INTRODUCTION

Acute ischemic stroke (AIS) is the most common type of stroke. It has the characteristics of high morbidity, high mortality and high disability, which seriously endangers the health and life of patients (Anna *et al.,* 2017). Effective treatment after AIS will directly affect the prognosis of patients (Gunaldi *et al.,* 2015). At present, recombinant tissue plasminogen activator alteplase (rtPA) has been widely used in many countries as the only thrombolytic drug that has been proved effective in the treatment of acute stroke in evidence-based medicine for patients within 3-4.5 hours of onset (Dai *et al.,* 2010; Benedetta *et al.,* 2017). However, after recanalization of occluded cerebral arteries, there will inevitably be brain reperfusion injury associated with rtPA, including hemorrhagic transformation or space-occupying brain edema (Hideharu *et al.,* 2016). The mechanism of hemorrhagic transformation may be related to vascular recanalization, reperfusion injury and collateral circulation establishment. Reperfusion injury tends to weaken or offset the benefits of thrombolytic therapy, and may even lead to worsening symptoms in patients (Ali *et al.,* 2017). How to solve the problem of reperfusion injury is the key to rtPA treatment. Immune inflammation plays a key role in the pathophysiology of AIS (Dindo *et al.,* 2004). Immune inflammatory signals are involved in all stages of post ischemic cascade reaction. Inflammation is an important factor in promoting hemorrhagic transformation and vascular edema reperfusion injury after thrombolytic therapy with rtPA within 4.5 hours of ischemic stroke (Hou *et al.,* 2015).

Fingolimod (FTY720), a sphingosine analogue, acts on sphingosine-1-phosphate receptor. After phosphorylation *in vivo,* it binds to S1P receptor on the surface of lymphocyte, changes lymphocyte migration, promotes lymphocyte to enter lymphoid tissue (Yusei *et al.,* 2016), prevents lymphocyte from leaving lymphoid tissue to enter peripheral circulation, and thus prevents these immune cells from immersing (Attari *et al.,* 2016). The central nervous system (CNS) is activated to achieve the effect of immunosuppression (Alejandro *et al.,* 2017). Therefore, we hypothesize that inhibiting inflammation may be beneficial to the treatment of reperfusion injury after thrombolysis in acute stroke (Justin *et al.,* 2016). Previous animal model tests and clinical validation tests showed that Fingolimod, as a new immunomodulator, could significantly reduce the enlargement of cerebral infarction and edema around hematoma after cerebral hemorrhage, protect BBB permeability and effectively improve the prognosis of patients (Hou *et al.,* 2015). However, the safety and efficacy of Fingolimod's early treatment in patients with AIS treated by intravenous alteplase thrombolysis (initial onset less than 4.5 hours) remain unknown (Inzucchi *et al.,* 2015). The aim of this study is to investigate the effects of alteplase intravenous thrombolysis combined with Fingolimod on the short-

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term and long-term clinical outcomes, primary and secondary endpoints of AIS patients and to explore its safety.

At present, alteplase thrombolytic therapy is the main method of early vascular recanalization, but due to the strict time window and the low recanalization rate of great artery occlusion, only a few patients can benefit. In order to reduce the risk, cerebrovascular guidelines recommend that traditional antiplatelet drugs such as aspirin enteric-coated tablets and clopidogrel bisulfate tablets should not be used within 24 hours after thrombolysis, which results in blind areas within 24 hours after thrombolysis. Therefore, searching for drugs that can be used in blind areas is an urgent problem at present. Experiments show that Fingolimod inhibits platelet activating factor receptor (PAFR) and inhibits platelet aggregation (Attari *et al.*, 2016). In this study, after intravenous thrombolytic therapy in patients with acute ischemic stroke, Fingolimod was added to continue the treatment to observe its efficacy and safety.

MATERIALS AND METHODS

General Information

This study selects 90 patients with acute ischemic stroke admitted in 2016. There were 57 males and 33 females, with an average age of (64.14 ± 11.65) years. All of them met the diagnostic criteria adopted by the Cerebrovascular Academic Conference and were confirmed by cranial CT (Computed Tomography) and/or MRI (Magnetic Resnane Iamge). They were randomly divided into 2 groups, 45 cases in each group. All patients were approved by ethics committee of our hospital, ethical approval number as 2015JZDH-ZL and all patients signed on the informed consent.

Inclusion Criteria

(1) Acute ischemic stroke was diagnosed clinically over the age of 18 years; (2) symptoms of neurological deficit were more than 30 minutes and did not alleviate before treatment; (3) there was no obvious disability [Rankin scale (mRS) score] < 1; and (4) patients signed informed consent.

Exclusion criteria

(1) There is a history of psychiatric or neurological diseases that may affect neurological assessment.(2) In the last three months, there are diseases that increase the risk of bleeding, such as severe liver diseases, ulcerative gastrointestinal diseases; (3) in the past, 10d underwent large operations with significant trauma or bleeding diseases. (4) Renal failure is defined as serum creatinine > 2.0g/L (177 Mmol/L) or glomerular filtration rate < 30mL (/min x 1.73m2). (5)Platelet count < 100 * 109/L. (6) Blood sugar level <2.8mmol/L or >22.2mmol/L. (7) Patients are being treated with oral anticoagulant drugs, such as Hua Falin, and the international normalized ratio >1.5. (8) Heparin was used within 48 hours, and activated partial thromboplastin time (APTT) exceeded the upper limit of laboratory normal value. (9)Suspicion of vascular occlusive disease is due to arterial dissection. (10) Pregnant women or patients are women of childbearing age and urine or blood is positive for beta -HCG.

Therapeutic method

The control group consisted of 45 patients, who were treated with alteplase for injection (German Brynger Ingelheim Company, specification 20 mL) intravenous thrombolysis. 10% of the patients were injected with alteplase (0.9 mg/kg) iv, the rest 90% were intravenously dripped with 250 mL saline within 1 hour. After 24 hours, the basic drugs for ischemic stroke (including anti-platelet aggregation, lipid lowering, scavenging oxygen free radicals, and nutritional nerve) were given.

The experimental group consisted of 45 patients who were given Fingolimod0.5 mg hard capsules after intravenous thrombolysis in the same way. Oral administration 1 times a day (0.5 mg). For 3 consecutive days, after thrombolysis, 24h was given the basic medicine for ischemic stroke.

Index detection

The NIHSS scores were recorded before treatment, 14 days and 90 days after treatment, and adverse events were recorded. After treatment, 14 and 90d were scored by the modified Rankin scale (mRS) 1 times, and the Barthel (Bl) index was 1 times. According to TOAST classification, two groups of patients were classified. The clinical efficacy of two groups of patients with different subtypes of acute ischemic stroke was observed. Cardiogenic embolism, other causes and unexplained causes of stroke were less. This study analyzed the clinical efficacy of patients with large atherosclerosis and small artery occlusion.

STATISTICAL ANALYSIS

SPSS19.0 software was used for statistical analysis. The measurement data conformed to the normal distribution expressed by x±s, and the non-normal distribution expressed by median. The chi-square test of two independent samples was used for comparison between groups. Two independent samples were tested by t test or nonparametric rank sum test. Measurement data were expressed as x±s, comparison between groups applied t test, count data were expressed as [n (%)] and tested by chi-square. When $P < 0.05$, the difference was statistically significant.

RESULTS

General data and clinical features

There were no significant differences in sex, age, history of hypertension, diabetes mellitus, history of coronary

heart disease, history of atrial fibrillation, baseline NIHSS score at admission and NIHSS score immediately after thrombolysis between the two groups as shown in table 1.

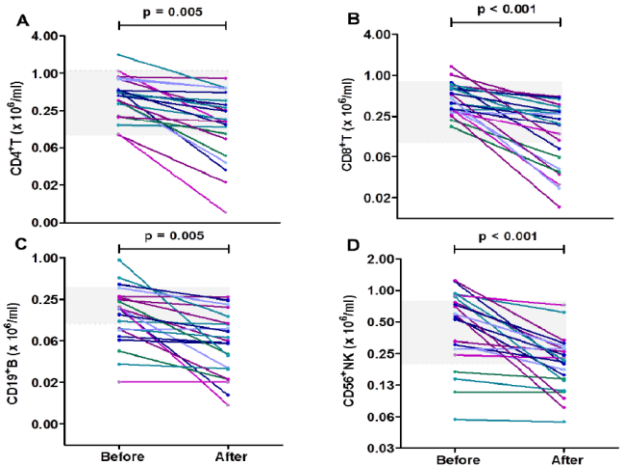

Fig. 1: Changes in CD4+T, CD8+T, CD19+B and CD56+ NK counts in circulating blood

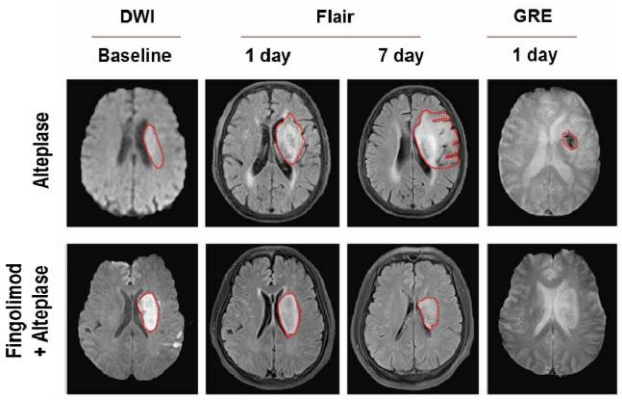

Fig. 2: MRI comparison of infarct volume, edema around the infarct and hemorrhagic transformation

Comparison of safety and efficacy after medication

After 14 days of treatment, there was no significant difference in NIHSS score, MRS score and Bi index between the two groups; after 90 days of treatment, the MRS index of the experimental group was lower than that of the control group (P<0.05), as shown in table 2.

Comparison of safety and efficacy after TOAST typing

The results showed that the NIHSS and mRS scores of the experimental group were significantly lower than those of the control group 90 days after treatment, and the BI index was significantly higher (P<0.05), while the scores of each scale of the patients with small-artery occlusion were not significantly different from those of the control group, as shown in tables 3 and 4.

Changes of lymphocyte in circulating blood after oral administration of Fingolimod

We used circulating lymphocyte counts to determine whether oral 0.5 mg Fingolimod has human drug activity. The rapid onset of Fingolimod (0.5mg) results in the decrease of blood lymphocyte, which makes it possible to treat AIS with alteplase intravenous thrombolysis.

At baseline, there was no significant difference in CD4 + T, CD8 + T, CD19 + B and CD56 + natural killer (NK) cell counts between alteplase group and combination group (fig. 1). The gray level merger area was alteplase treatment group, and the color line segment was combined with the combined treatment group. Monocytes were purified and stained by their respective antibodies to identify cell types. The percentage of CD4 + T lymphocyte (A), CD8 + T lymphocyte (B), CD19 + B cell (C) and CD56 + NK (D) was determined by flow cytometry, and the absolute number of all kinds of cells was determined by $*10^6$/ml. The value of each patient was mean + SE. Paired sample t test was used for comparison. 24 hours after oral administration of Fingolimod 0.5 mg, all kinds of lymphocytes in the peripheral circulation of the patients in the combined treatment group decreased steadily in varying degrees.

Comparison of MRI in two groups after thrombolytic therapy

Fig. 2 shows the contrast of infarct volume, periinfarct edema and hemorrhagic transformation between alteplase group (line 1) and combination group (line 2).

The upper and lower figs. in the first column show that there are infarcts in the basal ganglia and paraventricular area of the left middle cerebral artery in two patients at baseline. The size of infarcts is basically the same. One day after thrombolytic therapy, Flair showed that the lesion margin of the patients in the combined treatment group was clear and there was no obvious edema zone (fig. 2 below); the infarction margin of the patients in the alteplase group was blurred, indicating that edema around the lesion had begun to appear (fig. 2 above). At 7 days after thrombolytic therapy, Flair showed that the margin of infarction in the combined treatment group was still clear and the infarct volume was significantly smaller than that in the first day (lower fig. in column 3). In the alteplase group, the margin of infarction was blurred, the edema zone was visible around the lesion, and the volume of the lesion was significantly enlarged (upper fig. in column 3). There was no hemorrhagic transformation in the combined treatment group (fig. 4 below), and the GRE sequence in the alteplase group showed hemorrhagic transformation (fig. 4 above).

Complications and adverse events

No deaths, myocardial infarction, and recurrence of cerebral infarction occurred in the two groups. One case of hernia occurred in group alteplase, and decompressive craniectomy was performed in Department of cerebral surgery. No brain hernia occurred in the combined treatment group. Three patients in alteplase group had

gastrointestinal bleeding, while only one patient in combination group had gastrointestinal bleeding. The suspected pulmonary infection rate and urinary tract infection rate were 14% and 9% respectively in the combined treatment group, and 12% and 8% respectively in the alteplase treatment group. There was no statistical difference in the p value between the two groups.

DISCUSSION

At present, the treatment of AIS is still facing severe challenges (Kwabena *et al.,* 2016). Thrombolytic therapy with tissue plasminogen activator is still the only effective method at present, but due to the narrow time window of intravenous thrombolysis (3-4.5h), more contraindications and drug safety problems, less than 5% of patients can be treated (Katarzyna *et al.,* 2015; Jean *et al.,* 2017). Potential therapeutic targets include inhibition of ischemic cascade reaction, and inflammatory response plays a central role in ischemic cascade reaction (Kedar *et al.,* 2017). A large number of studies on rodent cerebral ischemia models have shown that inhibition of inflammatory response has unique therapeutic advantages. The time window for these treatments extends to 12-24h after cerebral ischemic stroke (Dindo *et al.,* 2004; Larsen *et al.,* 2013; Attari *et al.,* 2016). Therefore, for many patients who miss the thrombolytic time window, inhibiting early inflammatory response may improve clinical outcomes. Inflammatory injury after cerebral ischemia is closely related to ischemia-reperfusion. Inhibiting inflammation may be the most suitable supplement for reperfusion therapy, such as thrombolysis or arterial thrombectomy (Mohamed *et al.,* 2016).

For different targets of inflammatory response after cerebral ischemia, clinical studies of some drugs have been completed or are under way (Liu *et al.,* 2013). These include: (1) blocking antibodies to adhesion molecules (ICAM-1, MAC-1) or recombinant granulocyte inhibitors are ineffective in clinical trials. In phase III clinical trials of ICAM-1, the infarct volume and mortality of patients receiving anti-ICAM-1 monoclonal antibody (enlimomab) increased within 6 hours after ischemic stroke (Samia *et al.,* 2016). The negative results were attributed to the fact that the antibodies given to the patients came from mice, resulting in severe neutrophil and complement immune activation, which worsened the clinical results. (2) IL-1 receptor antagonist: IL-1ra has also been tested for the treatment of ischemic stroke. In a randomized, double-blind, controlled phase II a trial involving 87 patients, recombinant human IL-1ra has been shown to be safe, can pass BBB smoothly, and may be beneficial to the prognosis of ischemic stroke, especially in patients with cortical infarction. (3) Minocycline is a member of the tetracycline antibiotic family. Recently, it has been considered to have anti-apoptotic and anti-inflammatory effects, which can reduce microglia activation and MMP and NO production (Moumita *et al.,* 2015). The anti-apoptotic effect of minocycline derives from the inhibition of caspase-3, and its anti-inflammatory effect may be due to the inhibition of the activation of MAPK in microglia. Therefore, minocycline proved to protect the brain from ischemic damage and improve neurological dysfunction.

In this study, MRI was used to evaluate the efficacy of Fingolimod combined with alteplase in the treatment of AIS (Attari *et al.,* 2016). We found that Fingolimod combined with alteplase was superior to alteplase alone in terms of 24-hour main endpoint indicators, including changes in infarct volume, hemorrhage transformation and clinical improvement (Dindo *et al.,* 2004). In acute stroke studies, the assessment of disability status at 90 days (MRS score) is often used as the primary outcome. However, hemorrhagic transformation after thrombolytic therapy is usually an early event (<24 hours), and parenchymal edema often occurs 1-4 hours after the onset of ischemic stroke (Inzucchi *et al.,* 2015). In order to evaluate Fingolimod's biological efficacy, early brain tissue reperfusion injury after reperfusion needs to be assessed in a short time (Szewczyk *et al.,* 2015). Therefore, we use preliminary clinical results that may be most sensitive to reperfusion injury as the main endpoint. Long term clinical results can also be observed that patients in the combined treatment group are more likely to recover (Souich *et al.,* 2013).

Clinical factors such as higher NIHSS score after onset, delayed treatment, hypertension, atrial fibrillation, cerebral embolism, hyperglycemia and vascular recanalization can increase the incidence of hemorrhagic transformation (Schneider *et al.,* 2011). In this study, there was no significant difference in predictors of hemorrhagic transformation between the two groups, except for more patients with atrial fibrillation (8/22 and 2/25) in the fingolimod + alteplase combination therapy group. At baseline, because more patients have atrial fibrillation, it is predicted that fingolimod + alteplase patients will be more prone to hemorrhagic transformation than the control group (Yusei *et al.,* 2016). On the contrary, the incidence of hemorrhage transformation and severe symptomatic cerebral hemorrhage did not increase in the combined treatment group, and the hemorrhage rate and the severity of hemorrhage were lower than those in the control group (Zhang *et al.,* 2013). Therefore, our study shows that fingolimod can effectively prevent hemorrhagic transformation associated with alteplase thrombolytic therapy. In conclusion, this small sample study data suggest that Fingolimod is well tolerated and that combination therapy with alteplase within 4.5 hours of acute ischemic stroke may be safe. The safety, immune regulation and other non-immune-related effects of fingolimod in acute ischemic stroke need to be evaluated in larger clinical trials.

Table 1: Basic information of two groups of patients

Group	n/ case	Age / age	Male / case	Hypertension / case	Diabetes mellitus / case	Coronary heart disease / case	Atrial fibrillation / case	Admission baseline NIHSS score	Immediate NIHSS score after thrombolysis
Control group	45	65.46±11.70	26	26	10	9	9	3(0,18)	3.0(0,18)
Experimental group	45	63.31±11.65	31	26	16	13	6	4(0,19)	2.5(0,19)

Table 2: Comparison of short-term and long-term outcomes between the two groups (x± s)

Group	n/case	NIHSS score / points		MRS score / points		BI index / score	
		14d After drug use	90d After drug use	14d After drug use	90d After drug use	14d After drug use	90d After drug use
Control group	45	3(0,16)	3(0,14)	1.0(0,5)	1.5(0,5)	80(20,100)	80(20,100)
Experimental group	45	1(0,10)	1(0,10)	1.0(0,4)	1.0(0,3)	100(15,100)	100(20,100)

Table 3: Comparison of short-term and long-term outcomes between two groups of patients with atherosclerosis (x±s)

Group	n/case	NIHSS score / points		MRS score / points		BI index / score	
		14d After drug use	90d After drug use	14d After drug use	90d After drug use	14d After drug use	90d After drug use
Control group	22	4.5(0,16)	3.5(0,14)	2.0(0,5)	1.5(0,5)	7(20,100)	7(20,100)
Experimental group	26	3.5(0,14)	1.5(0,10)	2.0(0,4)	1.0(0,3)	8(20,100)	8(30,100)

Table 4: Comparison of short-term and long-term outcomes in patients with small-artery occlusion (x± s)

Group	n/case	NIHSS score / points		MRS score / points		BI index / score	
		14d After drug use	90d After drug use	14d After drug use	90d After drug use	14d After drug use	90d After drug use
Control group	12	0(0,4)	0(0,4)	0(0,2)	0(0,2)	10(70,100)	100(80,100)
Experimental group	20	1(0,5)	0(0,5)	1(0,2)	0(0,1)	100(85,100)	100(85,100)

CONCLUSION

In summary, fingolimod combined with alteplase intravenous thrombolysis for AIS does not affect alteplase thrombolytic effect. After intravenous thrombolysis with alteplase, 64% of the patients in the combined treatment group had vascular recanalization in varying degrees, and 68% of the patients in the alteplase group had occluded vascular recanalization. There was no difference in the recanalization rate between the two groups. 24 hours after oral administration of fingolimod (0.5 mg), CD4 + T, CD8 + T, CD19 + B and CD56 + natural killer cells in the circulating blood of the patients in the combined treatment group decreased steadily in varying degrees, and the decline trend lasted to the seventh day. The pharmacological effects of fingolimod were confirmed: changing lymphocyte migration, promoting lymphocyte to enter lymphoid tissue, preventing lymphocyte from leaving lymphoid tissue to enter the peripheral circulation, thus preventing these immune cells from infiltrating the central nervous system. It can inhibit the early inflammatory reaction after cerebral infarction. Fingolimod combined with alteplase intravenous thrombolysis for AIS can significantly inhibit the increase of lesion volume. After 1 day of intravenous thrombolytic therapy, compared with the baseline stage, the increase of infarct volume in the combined treatment group was significantly smaller than that in the alteplase treatment group (the main endpoint). At 7 days after thrombolytic therapy, the infarct volume of the patients in the combined treatment group was significantly smaller than that in the baseline stage (secondary endpoint).

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