Transcranial Pulsed Ultrasound with Alteplase Intravenous Thrombolysis for Vascular Recanalisation in Acute Ischemic Stroke

Zhenghong Chen¹ and Jingyu Zhang²

¹EEG Room, Linyi Central Hospital of Shandong Province, China

²Department of General Surgery, Linyi Central Hospital of Shandong Province, China

ABSTRACT

The objective of study was to investigate the effect of transcranial pulsed ultrasound combined with alteplase on treatment of vascular recanalisation in acute ischemic stroke patients. Eighty-two patients were randomly divided equally into two groups. Group A was treated with transcranial pulsed ultrasound combined with alteplase intravenous thrombolysis. Group B received alteplase intravenous thrombolytic treatment. At 2 and 24 hours after treatment, National Institutes of Health Stroke Scale (NIHSS) score of group A was lower than that of group B (both $p < 0.001$), and vascular recanalisation rate of patients in group A was higher than that of group B ($p = 0.004$, and 0.002 respectively). At 90 days after treatment, rate of favourable prognosis [(modified rankin scale (mRS) ≤ 2 points)] of group A was higher than that of group B ($p = 0.001$). Transcranial pulsed ultrasound combined with alteplase intravenous thrombolytic treatment can improve vascular recanalization rate and prognosis.

Key Words: Transcranial pulsed ultrasound, Acute ischemic stroke, Alteplase, Thrombolysis, Vascular recanalisation.

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Acute ischemic stroke is characterised by sudden onset of blood circulation to an area of the brain. Intravenous thrombolysis within the time window is an evidence-based treatment method that can improve the prognosis of patients with acute ischemic stroke.¹ Alteplase is an important intravenous thrombolytic agent conducive to the recanalisation of obstructed coronary artery through intravenous injection. However, simple thrombolysis has clinical application limitations due to its low vascular recanalisation rate and other problems.² A study have indicated that transcranial doppler ultrasound (TCD) can promote the recanalisation of occluded blood vessels.³ Transcranial pulsed ultrasound-assisted drug thrombolysis has drawn increasing attention from the society in recent years. The objective of this study was to investigate the effect of transcranial pulsed ultrasound combined with alteplase on the treatment of vascular recanalisation in patients with acute ischemic stroke.

This experimental study was carried out in Linyi Central Hospital of Shandong Province, China, from January 2017 to June 2019. This study was approved by the Hospital Ethics Committee. Eighty-two acute ischemic stroke patients with stenosis or occlusion of middle cerebral artery (MCA) were selected as the subjects of study. The inclusion criteria were patients who met the diagnostic criteria for ischemic stroke and diagnosed with stenosis or occlusion of MCA, and acute onset of less than six hours. Exclusion criteria were patients with cerebral hemorrhage, large cerebral infarction, contraindications for intravenous thrombolysis, severe organ dysfunctions of heart, liver, kidney, etc, blood pressure higher than 180/100 mmHg, abnormal blood coagulation and bleeding risk, pregnancy, and those with poor sonolucency of temple window. Eighty-two patients were randomly divided into group A and group B, 41 cases in each group. Patients in group A were treated with transcranial pulsed ultrasound combined with alteplase intravenous thrombolysis. Detailed therapeutic method was administration at 0.9 mg/kg, intravenous injection of 10% of the total dose initially within one minute, and dilution of the remaining 90% in 0.9% saline (250 mL), followed by continuous intravenous drip infusion for one hour. The method of transcranial pulse ultrasound treatment was that the ultrasonic probe of the transcranial ultrasound thrombolysis equipment was placed and fixed in the patient's coronary arteries. Parameter settings were time 30 minutes, pulse 0.5 second, repetition period one second, collimated beam frequency 800 kHz, sound intensity 0.75 W/cm^2 , duty ratio 1:2, and head area 3 cm^2 .

Correspondence to: Jingyu Zhang, Department of General Surgery, Linyi Central Hospital of Shandong Province, 276400, China

E-mail: pn6n18@163.com

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Table I: Comparison of clinical indexes in two groups.

Clinical indexes	Group A (n=41)	Group B (n=41)	p-value
NIHSS score before treatment (score)	15.56 ±2.30	15.61 ±2.67	0.927
NIHSS score at 2 hours after treatment (score)	11.67 ±1.38	13.89 ±1.85	<0.001
NIHSS score at 24 hours after treatment (score)	10.38 ±0.59	13.16 ±1.02	<0.001
Vascular recanalisation rate at 2 hours after treatment [n (%)]	19 (46.34)	7 (17.07)	0.004
Vascular recanalisation rate at 24 hours after treatment [n (%)]	23 (56.10)	9 (21.95)	0.002
Rate of favourable prognosis (mRS ≤2 points) at 90 days after treatment [n (%)]	26 (63.41)	11 (26.83)	0.001

Patients in group B received alteplase intravenous thrombolytic treatment. The alteplase intravenous thrombolytic treatment method was the same as that of group A. At the same time, transcranial pulsed ultrasound was used for comfort treatment. The probe of transcranial ultrasound thrombolysis equipment was placed in the patients' coronary arteries. Comfort treatment was performed by only turning on the machine and turning off the ultrasound probe.

The conditions of patients in two groups were evaluated before treatment, two hours after treatment, and 24 hours after treatment, by National Institutes of Health Stroke Scale (NIHSS).

Recanalisation was inspected using TCD. According to the TCD-TIBI (thrombolysis in brain ischemia) cerebral ischemia thrombolysis blood flow grading standard, the test results were divided into 6 grades. Patients with TIBI blood flow grade 0-1 were identified as vascular occlusion; the TIBI blood flow grade 2-3 was identified as partial recanalisation; and TIBI blood flow grade 4-5 was identified as complete recanalisation. Vascular recanalisation rate = (complete recanalisation + partial recanalisation) / total number of cases × 100%. Modified Rankin scale (mRS) was used to evaluate patients' prognosis at 90 days after treatment, and mRS ≤2 points was determined as good prognosis.

SPSS 25 software was used for statistical analysis. The count data were denoted as n (%), using Chi-square test. Measurement data were denoted as mean ± SD using an independent sample t test, $p < 0.05$ was considered statistically significant.

Among the 82 patients, there were 45 males (54.88%) and 37 females (45.12%), at the age of 46-72 (63.77 ± 3.82) years; there were 50 cases (60.98%) of proximal stenosis or occlusion of middle cerebral artery (MCA), 32 cases (39.02%) of distal stenosis or occlusion of MCA; blood glucose 6.23-9.01 (7.31 ± 0.82) mmol/L; systolic blood pressure 136-155 (147.36 ± 8.44) mmHg; diastolic blood pressure 80-95 (87.15 ± 5.09) mmHg. The time from onset to thrombolytic treatment was 240-273 (252.48 ± 12.76) minutes.

Before treatment, the difference in NIHSS score between two groups was not statistically significant ($p = 0.927$). At

two hours and 24 hours after treatment, NIHSS score of group A was lower than that of group B (both $p < 0.001$, Table I). At two hours and 24 hours after treatment, the vascular recanalisation rate of patients in group A was higher than that of group B ($p = 0.004$, 0.002 , respectively, Table I). At 90 days after treatment, the rate of favourable prognosis (mRS ≤2 points) of group A was higher than that of group B ($p = 0.001$, Table I).

Thrombolytic therapy is the main method for vascular recanalisation. However, under the influence of factors such as the timing of thrombolysis, the extent of coronary vessels, the degree of occlusion, and patient's physical condition, simple thrombolysis can rarely obtain desired therapeutic effect.⁴ One study indicated that ultrasound conductive to carotid artery thrombosis dissolution can also be used for thromboembolism prevention.⁵ A meta-analysis of six randomised and three non-randomised clinical studies of sonothrombolysis indicated that sonothrombolysis with high-frequency ultrasound almost triples the likelihood of complete recanalisation and doubles the odds of favourable functional outcome, at no increase in the risk of symptomatic intracerebral hemorrhage, in comparison to standard intravenous thrombolysis.⁶ Two other independent meta-analyses have also confirmed that sonothrombolysis appears to reduce death or dependency at 3 months and to increase recanalisation, without further augmenting the risk of symptomatic intracranial hemorrhage.^{5,6}

As shown in this study, compared to alteplase intravenous thrombolytic therapy, transcranial pulsed ultrasound combined with alteplase intravenous thrombolytic treatment can improve the vascular recanalisation rate of patients with acute ischemic stroke and improve the prognosis, which may be attributed to the fact that the combination of ultrasonic microfluidic effect, mechanical vibration, thermal effect, cavitation and sonication effect can effectively improve the blood circulation of the affected area; and enhance the effect of intravenous thrombolysis. In this study, patients with cerebral hemorrhage have not been found yet, which may be correlated with fewer case count included in the study.

In summary, transcranial pulsed ultrasound with the advantages of non-invasive and significant therapeutic effect can be optimised further with regard to parameter

setting and therapeutic methods in the future, so that it can be applied to clinical treatment of patients with acute ischemic stroke.

ETHICAL APPROVAL:

Ethical approval from the Ethical Committee of Linyi Central Hospital of Shandong Province Hospital in China was obtained.

PATIENTS' CONSENT:

Consents were taken from all patients.

CONFLICT OF INTEREST:

Authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

ZC: Design, data collection, data analysis and writing.

JZ: Writing, critical review and final approval.

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