CLINICAL STUDY ON ISCHEMIC PRECONDITIONING THERAPY ASSISTED WITH ULTRA-EARLY RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR THROMBOSIS IN THE TREATMENT OF ACUTE CEREBRAL INFARCTION PATIENTS

Hongmei He, Wenhui Kou, Huanhuan Wang, Shujing Ma, Haiyan Zhang, Yuan Zou, Xiuzhen Zhai, Qian Xue*
Department of Neurology, the First Affiliated Hospital of Hebei North University, Zhangjiakou, 075000, Hebei Province, PR China

ABSTRACT

Introduction: *To explore the clinical efficacy and safety of ischemic preconditioning therapy assisted with ultra-early recombinant tissue plasminogen activator (rt-PA) thrombosis in the treatment of acute cerebral infarction(ACI) patients.*

Materials and methods: *126 ACI patients admitted to our hospital from January 2021 to January 2022 were enrolled prospectively and divided into two groups using random number table method: the control group (63 cases) who were treated with ultra-early RT-PA thrombosis and the experimental group (63 cases) who were treated with ischemic preconditioning therapy on the basis of control group. 2 groups were compared in terms of the overall response rate, National Institutes of Health Stroke Scale (NIHSS) score, modified Rankin Scale (MRS) score, incidence of adverse reactions and follow-up Glasgow Outcome Scale (GOS) score before and after treatment.*

Results: *The overall response rate of the experimental group was significantly higher than that of the control group (P<0.05). The NIHSS score and Mrs score in the experimental group after treatment were significantly lower than those in the control group and before treatment (P<0.05). There was no significant difference between 2 groups in the incidence of adverse reactions (P>0.05). The good outcome rate based on follow-up GOS score in the experimental group was significantly higher than that in the control group (P<0.05).*

Conclusion: *Ischemic preconditioning therapy assisted with ultra-early RT-PA thrombosis can effectively promote the effect of disease control, protect neurological function and improve clinical outcome in ACI patients and have satisfactory safety.*

Keywords: *Ischemic preconditioning, recombinant tissue plasminogen activator, thrombolysis, acute cerebral infarction.*

DOI: 10.19193/0393-6384_2022_5_527

Received *March 15, 2022;* ***Accepted*** *June 20, 2022*

Introduction

Recombinant tissue plasminogen activator(rt-PA) thrombolytic therapy is recommended for acute cerebral infarction(ACI) patients conforming to the indications of intravenous thrombolysis by domestic and foreign guidelines[1], But patients who are admitted to the ultra-early stage, i.e., within 3 hours of onset, can soon realize cerebrovascular reperfusion through intravenous thrombolysis and prevent neurological injury in ischemic lesion, which is of great significance for the improvement the clinical outcome[2]. Nevertheless, previous studies have shown that the recanalization rate of blood vessels remains low after rt-PA thrombolytic therapy. As a result, there are quite a few patients who are not significantly improved in neurological function and even show hemorrhagic transformation[3]. In recent years, ischemic preconditioning therapy has been widely used in clinical practice and showed a good effect in the protection of cardio and cerebrovascular functions[4]. Based on the above evidence, we

analyzed the clinical efficacy and safety data of 126 ACI patients admitted to our hospital from January 2021 to January 2022 prospectively, and compared the differences between thrombolytic therapy alone and thrombolytic therapy combined with ischemic preconditioning therapy in clinical benefits, with a view to offer more reference for the use of combined therapy.

Materials and methods

General data

126 ACI patients admitted to our hospital from January 2021 to January 2022 were enrolled prospectively and divided into the control group and experimental group using random number table method, with 63 cases in each group. In the control group, there were 40 males and 23 females, aged 48~65, with an average age of (53.86±6.25).

The duration from onset to treatment was 2~3h, with an average of (2.33±0.48)h. According to the dosage of rt-PA, there were 9 cases for 0.6mg/kg and 54 cases for 0.9mg/kg. According to the classification standard of ischemic stroke in China, there were 24 cases of large artery atherosclerosis stroke, 14 cases of cardiogenic stroke, 13 cases of perforating artery stroke and 12 cases of other etiologies. According to the type of concurrent underlying diseases, there were 24 cases of hypertension, 19 cases of hyperlipidemia and 16 cases of diabetes. In the experimental group, there were 42 males and 21 females, aged 46~64, with an average age of (53.19±6.07).

The duration from onset to treatment was 2~3h, with an average of (2.44±0.53)h. According to the dosage of rt-PA, there were 11 cases for 0.6mg/kg and 52 cases for 0.9mg/kg. According to the classification standard of ischemic stroke in China, there were 27 cases of large artery atherosclerosis stroke, 17 cases of cardiogenic stroke, 11 cases of perforating artery stroke and 10 cases of other etiologies. According to the type of concurrent underlying diseases, there were 26 cases of hypertension, 17 cases of hyperlipidemia and 18 cases of diabetes.

Inclusion, exclusion and elimination criteria

Inclusion criteria:

- Diagnosed with ACI clinically;
- The duration from onset to treatment was <3h;
- With contraindication for rt-PA therapy;
- Aged 18~65.

Exclusion criteria:

- Heart, liver and kidney insufficiency;
- Cognitive disorder or psychiatric disorder;
- Hemorrhagic tendency;
- Oral anticoagulant in the last 4 weeks;
- History of severe craniocerebral trauma, suspected subarachnoid hemorrhage or intracranial hemorrhage;
- Deep venous embolism in lower limbs; allergic constitution.

Therapeutic method

Both groups underwent symptomatic interventions, such as anticoagulation, lipid regulation, antihypertension, antihyperglycemic, correction of electrolyte disorder and nutritional support, for 21 consecutive days. The control group was treated with ultra-early rt-PA thrombolysis with a dosage of 0.6/0.9mg/kg and a maximum dosage of 90mg. To begin with, 10% of the total dosage was injected intravenously within 1min, and the remaining 90% was added to sodium chloride solution, 0.9% in 100ml, and dripped intravenously for 1h. The experimental group was treated with limb ischemia preconditioning on the basis of the control group, that is, the brachial artery in one limb of the patients was compressed with the cuff of sphygmomanometer.

Distal ischemia was established after inflating for up to 200mmHg and lasted for 5 min. After that, distal reperfusion was established after deflating for 5 min for 3 consecutive cycles, once a day for 7 consecutive days.

Observation indicators

The efficacy was evaluated by the standard of Chinese Neuroscience Society, and divided into 4 grades: complete response, marked response, response and no response.

Overall response rate=complete response+ marked response+ response; NIHSS was adopted to evaluate the degree of neurological deficit, and the higher score, the more severe neurological deficit[5]; Mrs scale was adopted to evaluate activities of daily living (ADLs), with a score of 1~6.

The higher score, the worse ADLs[6]; the occurrence of adverse reactions during treatment was recorded, including limb pain, subcutaneous hemorrhage, hematuria, and nausea; clinical outcomes were assessed 6 months after treatment. And they were divided into recovery, mild disability, severe disability, vegetative state and death, according to GOS scale[7]. Good outcome = recovery+ mild disability.

Statistical processing

SPSS 21.0 software was selected to process the data. Measurement data were compared by using t-test and expressed as ($\bar{x}\pm s$), while enumeration data were compared by using χ^2 test and expressed as a percentage, with $P<0.05$ indicating that the difference was statistically significant.

Results

Comparison between two groups in overall response rate

The overall response rate of the experimental group was significantly higher than that of the control group ($P<0.05$). See Table 1.

Group	Number of Cases	Complete Response	Marked Response	Response	No Response	Overall Response Rate (%)
Control Group	63	20	17	14	12	80.95
Experimental Group	63	31	20	10	2	96.83*

Table 1: Comparison between Two Groups in Overall Response Rate.
**P<0.05 compared with the control group.*

Comparison between two groups in NIHSS score and mrs score before and after treatment

The NIHSS score and Mrs score in the experimental group after treatment were significantly lower than those in the control group and before treatment ($P<0.05$). See Table 2.

Group	Number of Cases	NIHSS Score		MRS Score	
		Before Treatment	3 Weeks After Treatment	Before Treatment	3 Weeks After Treatment
Control Group	63	12.85±1.87	9.40±1.54△	5.70±1.48	4.15±1.07△
Experimental Group	63	12.72±1.81	7.18±1.27△*	5.62±1.43	3.98±0.74△*

Table 2: Comparison between Two Groups in NIHSS Score and Mrs Score Before and After Treatment (pts).
**P<0.05 compared with the control group, P<0.05 compared with before treatment.*

Comparison between two groups in adverse reactions

There was no significant difference between 2 groups in the incidence of adverse reactions ($P>0.05$). See Table 3.

Comparison between two groups in outcome based on follow-up GOS score

The good outcome rate based on follow-up GOS score in the experimental group was significantly higher than that in the control group ($P<0.05$). See Table 4.

Group	Number of Cases	Limb Pain	Subcutaneous Hemorrhage	Hematuria	Nausea	Incidence of Adverse Reactions (%)
Control Group	63	0	2	1	1	6.35
Experimental Group	63	2	3	1	1	9.52

Table 3: Comparison between two groups in adverse reactions.

Group	Number of Cases	Recovery	Mild Disability	Severe Disability	Vegetative State	Death	Good outcome Rate (%)
Control Group	63	28	18	13	3	1	73.01
Experimental Group	63	36	24	3	0	0	95.24

Table 4: Comparison between Two Groups in Outcome Based on Follow-up GOS Score.
**P<0.05 compared with the control group.*

Discussion

ACI is one of the common acute and severe diseases in the Department of Neurology. Patients suffer from atherosclerosis and thrombosis in their cerebral blood supply due to multiple factors alone or jointly, which results in interrupted blood flow, luminal stenosis and even occlusion, and eventually neurological deficit and laloplegia. This put a heavy burden on their family and society[8-10]. Early intravenous thrombolysis has become a preferred therapeutic regimen for ACI patients that conform to indications, which shows certain efficacy in the improvement of clinical out-come. But there are still quite a few patients with insignificant improvement in neurological function and no recanalization, and even hemorrhagic transformation and reperfusion injury in severe cases[11, 12]. How to further promote the effect of ultra-early intravenous thrombolysis and significantly improve the clinical outcome of ACI patients has become one of the hot issues in the medical community.

As an organ related to the human central nervous system, the brain is extremely sensitive to ischemic state because of its abundant blood supply, histological structure and function. When ischemia-reperfusion injury occurs, the patients are prone to injuries in cerebral oxygenation function and brain tissues[13]. Previous studies have shown that in situ ischemic preconditioning of important tissues and organs of the body can easily damage target cells, especially nerve cells, while limb ischemic preconditioning intervention is safer, with dominant

advantages in the improvement of the tolerance of important organs, such as heart, brain and lung to ischemic injury[14, 15]. Other reports have confirmed that short-term and multiple limb ischemic preconditioning can activate the endogenous protective mechanism in human body, regulate from nerves, body fluids and other aspects in an all-round way, mobilize the multi-target endogenous protective factor, mitigate the damage of brain tissues, alleviate or avoid the occurrence of cerebral ischemia-reperfusion injury[16-18].

It has such advantages as easy-to-operate and non-invasive. What's more, ischemic preconditioning has been proved to alleviate or delay apoptosis of axoneurons, and be able to protect neurological function through related targets of Notch1 neuronal pathway[19]. From the results of this study, the overall response rate in the experimental group was significantly higher than that in the control group. The NIHSS score and Mrs score in the experimental group after treatment were significantly lower than those in the control group and before treatment, which substantiates that ischemic preconditioning therapy can help improve the effect of disease control, and better protect neurological function in ACI patients.

Previous studies have indicated that limb ischemic preconditioning can enhance local or systemic tolerance to ischemia-reperfusion injury through transient ischemic stimulation. And the effect of this therapy on multiple neural signal transduction pathways including nerves and body fluids can also build up resistance to ischemia-reperfusion injury of important tissues and organs. This is of great significance for the improvement of the clinical outcome of patients[20, 21].

According to the results of this study, the good outcome rate based on follow-up GOS score in the experimental group is significantly higher than that in the control group, which supports the above viewpoint. What's more, there is no significant difference between two groups in the incidence of adverse reactions, which further suggests that the safety of ischemic preconditioning therapy assisted with ultra-early RT-PA thrombosis in ACI patients is worthy of recognition, which is consistent with previous reports[22, 23]. In summary, ischemic preconditioning therapy assisted with ultra-early RT-PA thrombosis can effectively promote the effect of disease control, protect neurological function and improve clinical outcome in ACI patients and have satisfactory safety.

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Acknowledgement:
Fund Project: Medical science research topics of Hebei Provincial Health Commission in 2019 (no.20190881).

Corresponding Author:
Qian Xue
Department of Neurology, the First Affiliated Hospital of Hebei North University, Zhangjiakou, 075000, Hebei Province, PR China
Email: xueqian6166@163.com
(China)