

The clinical study on the treatment for acute cerebral infarction by intra-arterial thrombolysis combined with mild hypothermia

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Abstract. – OBJECTIVE: This study was purposed to evaluate the clinical efficacy of the treatment for acute cerebral infarction by intra-arterial thrombolysis combined with mild hypothermia.

PATIENTS AND METHODS: Thirty patients, diagnosed with acute anterior circulation cerebral infarction and admitted to the Hospital between January 2013 and September 2015, were randomly divided into the control group and the mild hypothermia group, each group comprising 15 cases. The treatment of intra-arterial thrombolysis combined with mild hypothermia was administered to the mild hypothermia group, while only the treatment of intra-arterial thrombolysis was performed on the control group. The National Institutes of Health Stroke Scale (NIHSS) score, Modified RANKIN Scale (MRS) score, cerebral hemorrhage transformation, pulmonary infection, and the incidence of gastrointestinal bleeding of the two groups were compared on day 14, 30, and 90 following the onset of the disease.

RESULTS: The prognosis (MRS score) of the group with mild hypothermia combined with intra-arterial thrombolysis was lower than that of the group treated only with intra-arterial thrombolysis ($p < 0.05$). The incidence of cerebral hemorrhage transformation of the group with mild hypothermia combined with intra-arterial thrombolysis was also lower than that of the control group ($p < 0.05$). There was no significant difference in the incidence of pulmonary infection and gastrointestinal bleeding between the two groups.

CONCLUSIONS: Treatment of patients suffering from acute cerebral infarction by means of intra-arterial thrombolysis in combination with

mild hypothermia can result in reduced risk of hemorrhagic transformation and improve clinical outcome.

Key Words:

Cerebral infarction, Mild hypothermia, Intra-arterial thrombolysis, Cerebral hemorrhage transformation.

Introduction

Acute cerebral infarction is a disease with high rates of incidence, mortality and disability, which accordingly, is a grave threat to human health. Rapid thrombolysis and cerebral protection are two essential steps in the treatment of cerebral infarction. However, this simple revascularization cannot guarantee positive clinical effects. On the other hand, mild hypothermia therapy has proved beneficial to cerebral protection in animal models of stroke. Clinical studies confirmed that it is also an effective treatment for patients experiencing cardiac arrest and new brain tissue injury caused by hypoxia¹⁻³. Since Busto et al⁴ first proposed the efficacy of mild hypothermia therapy on acute cerebral infarction in 1987, there have been many reports confirming the validity of hypothermia therapy as a treatment. The question that can be proposed is: could administer the more conventional arterial thrombolysis treatment in combination with mild hypothermia result in a synergistic effect? Many animal experiments have achieved encouraging results, but the clinical

cal reports are relatively few. In recent years, we have achieved satisfactory curative effect upon treating patients with acute cerebral infarction by intra-arterial thrombolysis combined with mild hypothermia.

Patients and Methods

Patients

The patients with acute cerebral infarction were admitted to the Neurology Department of our Hospital and were administered thrombolytic therapy, in which 30 patients satisfied the inclusion criteria, with 30 cases involving male subjects and 15 cases involving females. Their ages ranged from 55 to 85 years old, with the average age being 66.42. Inclusion criteria: (1) the MRS score was 0 or 1 before stroke; (2) acute ischemic stroke; (3) not accepted for r-tPA intravenous thrombolysis; (4) the infarction was caused by internal carotid artery and occlusion of the M1 segment of the artery in proximal brain; (5) NIHSS score ≥ 6 ; (6) age ≥ 18 ; (7) 6 h > disease time > 4.5 h; (8) The informed consent was obtained from the patients. Exclusion criteria: to reduce the difference of prognosis caused by the arterial failure, cases in which the intra-arterial thrombolytic therapy failed to achieve revascularization were excluded. Severe congestive heart failure, unstable angina pectoris, as well as intracranial tumor, hemorrhage, pregnancy, and hemodynamic instability under CT scan were also excluded. Additional exclusions included severe thrombocytopenia, pre-existing neural function defect (MRS ≥ 2), cases in which the infarction size exceeded 1/3 MCA blood supply area.

Methods

In 2015, the American Heart Association (AHA) and the American Stroke Association (ASA) released a new version of the early management guidelines for acute ischemic stroke, which recommends that intra-arterial thrombolysis can be conducted for appropriate patients to restore blood vessels for blood flow reperfusion as soon as 6 h after the onset of disease. Accordingly, conventional therapy was conducted on the control group: the treatment was performed in accordance with the guidelines, which includes the ancillary drug used for the deprivation of body fluids and reduction of intracranial pressure, the drug for improving blood circulation, as well as the acid-inhibitory drug used to prevent

upper gastrointestinal bleeding and pulmonary infection and to control blood sugar, blood pressure, and other complications. After endovascular treatment, the mild hypothermia group was immediately treated with mild hypothermia, which made use of a temperature-regulating blanket with circulating water to cool the body of the patient, while the head was treated with an electric ice cap. 1.5 h before starting, 25 mg of Wintermin and 25 mg of Phenergan were administered through intramuscular injection to rapidly induce sleep and prevent shivering. At the same time, lytic cocktail (50 ml NS + 50 mg Phenergan + 50 mg Wintermin) was continuously pumped into the patient. At the start, it was pumped at a rate of 7-8 ml/h, then the dosage and drop rate were adjusted according to the heart rate, blood pressure, and degree of shivering of the patient, with the general maintenance dose of 5 ml/h. This treatment reduced the rectal temperature of the patient below 35°C in 12 h. This temperature was then maintained at 33-34°C. The rectal temperature was rewarmed after maintaining mild hypothermia for 5 days. The shivering that occurred during this period of hypothermia therapy could be controlled by providing pethidine through intramuscular injection. Finally, the rewarming method⁵ at a rate of around 0.2°C/h was adopted to increase the rectal temperature of the patient to 36.5°C-37.5°C.

Index Observing and Evaluation of Curative Effect

Thirty patients were randomly divided into two groups: the mild hypothermia group and the control group. In the mild hypothermia group, there were 8 males, 7 females, 11 cases of hypertension, 8 cases of type-2 diabetes mellitus, 13 cases of hyperlipidemia, 13 cases of internal carotid artery infarction (revealed by cerebral angiography after being admitted to the hospital), and 2 cases of middle cerebral artery infarction. In the control group, there were 7 males, 8 females, 12 cases of hypertension, 6 cases of type-2 diabetes mellitus, 12 cases of hyperlipidemia, 11 cases of internal carotid artery infarction (revealed by cerebral angiography after being admitted to hospital), and 4 cases of middle cerebral artery infarction (Figures 1, 2). Blood analysis, blood coagulation routine, brain CT and ECG examination were conducted immediately after being admitted to the hospital. All patients underwent 24 h of ECG monitoring to scan for myocardial enzymes. The pulmonary infection



Figure 1. The image of **(A)** arterial occlusion of right cerebral, and **(B)** artery of right cerebral after arterial thrombolysis.

could be detected early through clinical auscultation, increased white blood cell count, and a chest X-ray. Key indicators were CRP > 10 mg/L or white blood cells > 11.0 E9/L. The chest X-ray was conducted to confirm the initial suspicion of pulmonary infection, and the anti-infective drug

was given after diagnosis. Hemorrhaging of the gastrointestinal tract was determined by pumping back the gastric content with a nasogastric tube. CT examination of the brain was conducted to observe whether hemorrhagic transformation and cerebral edema occurred at 24 h and day 7 after

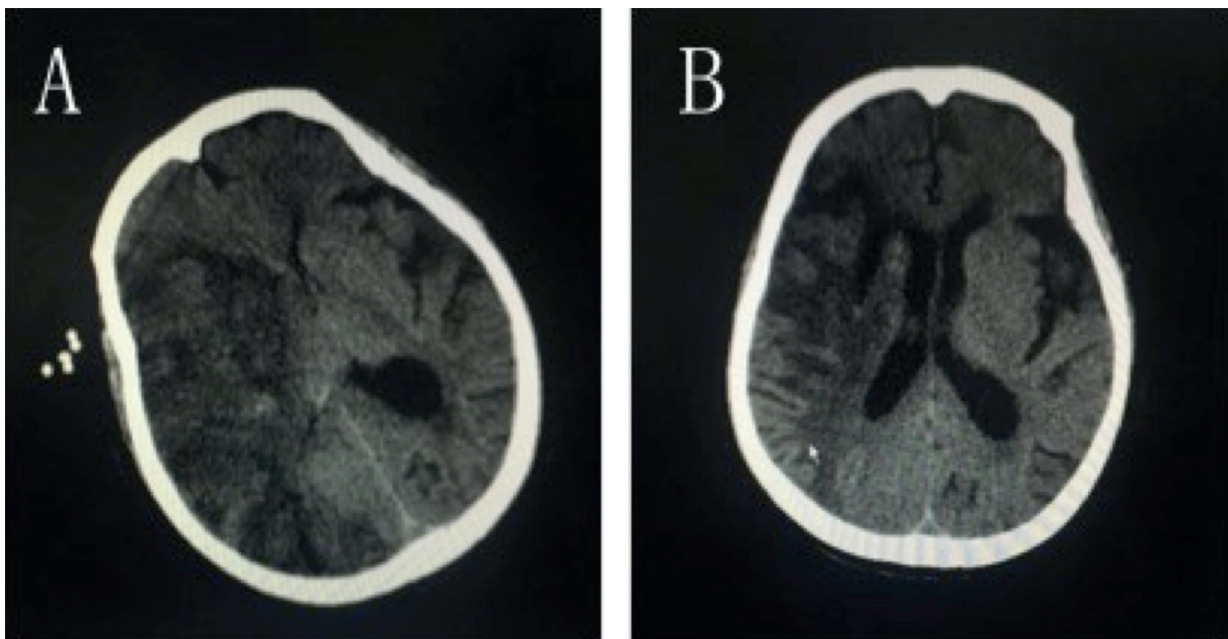


Figure 2. The CT of right cerebral showed **(A)** low-density focus before treatment, and indicated **(B)** reduced low-density focus after conventional therapy.

being admitted to the hospital. If a few bleeding spots were found around the infarction, the hemorrhage within the infarct area was classified as hemorrhagic transformation. Hemorrhagic transformations were divided into 4 types. In the first type of hemorrhagic infarction, there was a small amount of bleeding spots around the infarct. In the second type of hemorrhagic infarction, hemorrhagic fusion was observed within the infarct area. In the first type of parenchyma hematoma, the hematoma was $< 30\%$ of the infarct size. In the second type of parenchyma hematoma, the hematoma was $> 30\%$ of the infarct size⁶. Blood pressure was maintained at $< 185/105$ mmHg during hypothermia therapy. Urapidil was administered if the blood pressure rose above this level, and noradrenaline was provided to treat low blood pressure. Blood glucose levels were stabilized in the range of 8 mmol/L-10 mmol/L. If the blood glucose level rose above this level, it was treated by injecting insulin under the skin. Blood potassium, sodium, and chlorine levels were also monitored and maintained at a normal range. The complications experienced by patients in the two groups were compared to evaluate the safety of endovascular treatment combined with mild hypothermia therapy. The efficacy evaluation was performed according to the MRS score on day 14, 30, and 90 after the onset of disease.

Statistical Analysis

The data was analyzed using SPSS 16.0 software (SPSS Inc., Chicago, IL, USA), and the continuous variables were represented by mean $\pm$ standard deviation. The enumeration data between two groups adopted Fisher exact probability. The continuous data at different time points adopted repeated measure ANOVA, and the inspection level of $\alpha \pm 0.05$. A value of $p < 0.05$ confirmed that the difference was statistically significant.

Results

There were no significant differences in age, sex ratio, severity of the disease, concomitant disease, anamnesis, and other clinical data of the patients between the two groups, as determined through statistical analysis, and the materials have good comparability (as seen in Table I).

Discussion

Massive cerebral infarction is a widely spreading ailment with a high mortality rate, and represents a significant threat to human life and life quality. Thus, early treatment for cerebral infarction is crucial. The earlier it is treated, the better the prognosis will be. Rapid thrombolysis and early cerebral protection are two important steps in the treatment of cerebral infarction. Simple thrombolytic therapy alone cannot guarantee clinical efficacy, leading to much research on the application of brain-protective measures. In clinical practice, mild hypothermia therapy, which was applied to treat newborns with cardiac arrest and hypoxia, as well as patients with craniocerebral trauma or acute stroke, is now considered, by expert consensus, having a neuroprotective effect. In 2015, Imataka et al⁷ applied mild hypothermia to treat patients with cerebral infarction for the first time, and the results revealed that mild hypothermia could reduce the high intracranial pressure observed in the early stage of cerebral infarction. Preliminary clinical studies have shown that hypothermia therapy is beneficial in brain-protective therapy of local ischemia⁸⁻¹⁰. Currently, the treatment of mild hypothermia combined with intra-arterial thrombolysis is applied for patients with acute cerebral infarction at home, rather than in a clinical environment. Thus, the available clinical data from this combination therapy is extremely limited.

Table I. Comparison of baseline data between the mild hypothermia group and the control group.

	Mild hypothermia group	Control group	t/ χ^2	p
Male/female (case)	8/7	7/8		1.0
Average age (year)	63.33 $\pm$ 9.81	68.26 $\pm$ 9.53	1.40	0.1733
Disease time (hour)	4.66 $\pm$ 0.54	4.81 $\pm$ 0.35	0.877	0.3878
MCAO/CAO (case)	2/13	4/11		0.651
Neurologic impairment score at admission	15.93 $\pm$ 3.94	14.93 $\pm$ 4.30	0.6643	0.5119

The mild hypothermia has the effect on general vital signs.

Intra-arterial thrombolytic therapy can result in rapid revascularization, but it is also known to cause complications such as massive releasing of free radicals and calcium overload, as well as leading to a series of acute inflammatory cascades, aggravating brain tissue damage. Animal experiments have shown that mild hypothermia inhibits these inflammatory responses in a variety of ways, so as to play a role in cerebral protection. The existence of this cerebral protective effect ensures that early impairment scores of patients with mild hypothermia will be lower than those in the control group. Through a careful clinical study of this group, it was found that the neurologic impairment score and MRS score of the mild hypothermia group decreased pronouncedly after treatment, and $p < 0.05$ in the mild hypothermia group, as compared with the control group (Figure 3). These findings indicate that combined treatment of mild hypothermia with intra-arterial thrombolysis can contribute to the recovery of neurologic impairment. Also, the rate of cerebral hemorrhage transformation of the mild hypothermia group is drastically lower than that of the control group, and the prognosis is significantly improved. Three main factors influencing the curative effect of mild hypothermia are: (a) the start time of mild hypothermia; (b)

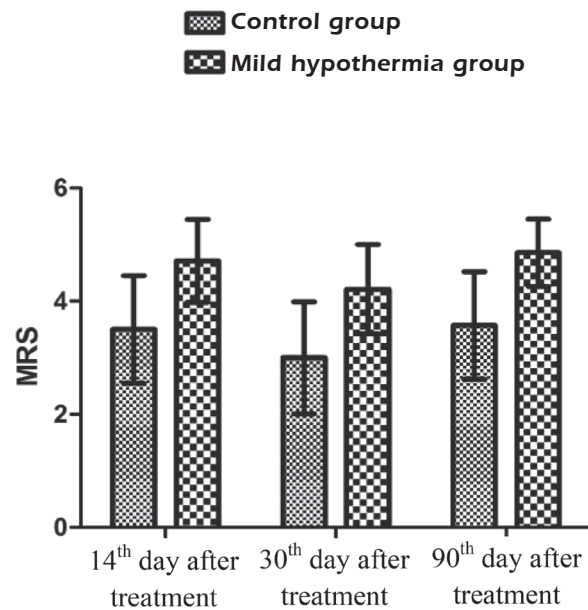


Figure 3. Neurologic impairment score and prognosis between two groups are significantly different.

the maintenance time of mild hypothermia; (c) the time of revascularization. The start time of mild hypothermia is crucial. Most of the studies suggest that the earlier the mild hypothermia is

Table II. Changes of BP, HR, and R before and after mild hypothermia therapy.

Index	Before mild hypothermia	The stationary phase of mild hypothermia	After rewarming	F	p
BP	141.00 ± 10.98	132.69 ± 10.81	131.69 ± 13.10	2.71	0.0865
HR	81.69 ± 13.55	73.62 ± 14.78	76.84 ± 13.13	7.06	0.0039
R	17.92 ± 0.86	17.69 ± 0.63	17.62 ± 0.87	0.48	0.6246

Before and after mild hypothermia therapy, the vital signs are stable, and the blood pressure, heart rate and respiration are not significantly different.

Table III. Complications experienced by the mild hypothermia group and the control group.

Groups	Upper gastrointestinal bleeding	Pulmonary infection	Venous thrombosis	Cerebral hernia	Arrhythmia	Cerebral hemorrhage transformation
Mild hypothermia group	6	8	3	2	1	1
Control group	4	6	1	6	3	6
p	0.700	0.715	0.598	0.215	0.598	0.030

The common complications are upper gastrointestinal bleeding, pulmonary infection, venous thrombosis, cerebral hernia, arrhythmia, and cerebral hemorrhage transformation, and there was no significant difference between the two groups. The rate of cerebral hemorrhage transformation in the mild hypothermia group was lower than that in the control group, and this difference is statistically significant. The deaths of 3 patients in the hypothermia therapy group include one patient who died after invalid salvage therapy because of the occurrence of ventricular tachycardia during the treatment, and the other 2 cases perished from cerebral hernia. There are fewer cases of cerebral hernia in the mild hypothermia therapy group but without statistical significance.

Table IV. Comparison of mortality.

Groups	N	Death	Mortality
Mild hypothermia group	15	3	20%
Control group	15	4	27%
<i>p</i>		1.00	

There is no significant difference in mortality between the two groups.

Table V. Comparison on neurologic impairment score of patients between two groups.

Groups	Before treatment	One month after treatment	F	<i>p</i>
Mild hypothermia group	16.08 ± 4.06	7.50 ± 4.056	63.799	< 0.001
Control group	14.64 ± 2.73	9.27 ± 2.05		
F		0.022		
<i>p</i>		0.884		

conducted after cerebral ischemia, the better the curative effect will be. However, in clinical practice, many patients are not in the hospital when they are attacked by disease. A considerable number of patients are treated for several hours after the onset of the disease. At the same time, an additional question also needs to be considered: is there synergistic action of the combination of thrombolytic drug and mild hypothermia? The effect of the combined treatment needs to be studied. Mild hypothermia has obvious influence on thrombolytic drug and endogenous anticoagulant activity. Currently, a frequently used thrombolytic drug, at home and abroad, is recombinant tissue plasminogen activator (rt-PA), an activator whose mechanism of action involves plasmin. Plasmin is a temperature-dependent enzyme, which consequently is affected by hypothermia. The dissolution of the blood clot changes with temperature. Upon raising body temperature by 1°C, the Rt-PA increases the dissolution of the blood clot of 0.5%. In the animal experiments of Staikou et al¹¹, it was discovered that maintaining a state of hypothermia at 32°C resulted in

decreased endogenous anticoagulant activity and increased activity of fibrinolytic proteins such as plasminogen and antiplasmin. Premature mild hypothermia therapy may delay the start time of intravenous and intra-arterial thrombolysis and affect the dissolution of rt-PA to the thrombus. From animal studies¹², it can be found that, even if mild hypothermia starts at 6 h after ischemia, it still has a neuroprotective effect if the mild hypothermia treatment is maintained for 12-48 h. Therefore, we believe that the early thrombolysis reflow is more important than the mild hypothermia therapy. Mild hypothermia is advocated to commence immediately after thrombolysis, rather than before thrombolysis. Our study dictates that mild hypothermia therapy is performed immediately after intra-arterial thrombolysis. After ischemic stroke, the optimal maintenance time of hypothermia is still uncertain. In clinical practice, the ischemia time of ischemic stroke is relatively long, and the drug or interventional operation are needed to ensure revascularization, so it seems necessary for patients with stroke to prolong the process of hypothermia. The deterioration of

Table VI. The comparison on the MRS score of patients between two groups after treatment.

Groups	14 th day after treatment	30 th day after treatment	90 th day after treatment	F	<i>p</i>
Mild hypothermia group	3.50 ± 1.65	7.50 ± 4.056	3.57 ± 1.65	7.36	0.002
Control group	4.71 ± 1.27	9.27 ± 2.05	4.85 ± 1.03		
F		5.69			
<i>p</i>		0.025			

clinical symptoms is mainly caused by ischemic stroke and hemorrhagic transformation, which mostly occurs during the 2-5 days after stroke^{13,14}. Long-term hypothermia therapy can reduce the intracranial pressure and improve the clinical prognosis, but shows no difference in the complications observed¹⁵. Interestingly, the rewarming after short-term hypothermia therapy can cause the rebound of intracranial pressure, which never occurs in long-term hypothermia therapy. There are studies indicating that long-term maintenance time seems to mean better neuroprotective effect. If the hypothermia therapy starts later (a few hours after the onset of disease), it tends to need longer maintenance time⁷. Rewarming after maintaining the hypothermia for 5 days cannot only guarantee the cerebral protection during the peak time of cerebral edema and cerebral hemorrhage transformation, but also reduce the incidence of complications that may be caused by prolonged mild hypothermia. Generally, in clinical practice, the mild hypothermia condition is achieved in 12-24 h and maintained for 24-72 h⁹⁻¹¹. Some scholars¹⁶ have also proposed that the maintenance time should be prolonged to a week or even longer to further control cerebral edema. Due to a series of side effects caused with the prolonging of hypothermia time, this study recommends an average maintenance time of hypothermia therapy of 5 days, which will not cause severe complications while achieving desired curative effect. During the mild hypothermia therapy, common clinical complications were observed included bradycardia, pulmonary infection, and blood coagulation disorders. The most common complication in this study was pulmonary infections, which was consistent with the reported results of Zhu et al¹⁷ and Yenari et al¹⁸. There was no significant difference observed upon comparison with control group ($p > 0.05$). Consequently, in clinical practice, we recommend that this treatment should include anti-infective therapies, such as sputum suction, aerosol inhalation, and administration of antibiotics.

Conclusions

This study has revealed that, if the thrombolysis reflow is rapidly conducted and the mild hypothermia is performed as soon as possible after cerebral ischemia, with maintenance of hypothermia for a relatively long time, and blood vessel reperfusion as soon as possible, a better

prognosis is likely¹⁹⁻²². The application of mild hypothermia therapy in ischemic stroke treatment has been gradually extended. In clinical practice, there are some practical issues that still need to be addressed, such as slowly carrying out the cooling and rewarming, electrolyte monitoring, and the maintenance time of cooling. Also, the sample size in this study was small. An expanded sample size will be required for future studies.

Ethical Approval

The research was conducted in accordance with the Declaration of Helsinki and the United National Institutes of Health.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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