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Effect of Remote Ischemic Conditioning Combined with Arterial Thrombolysis on Patients with Ultra-Early Cerebral Infarction

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Abstract: *Objective:* To observe the effect of remote ischemic conditioning + arterial thrombolysis in patients with ultra-early cerebral infarction. *Methods:* 60 patients with ultra-early cerebral infarction were used as samples, and this study was carried out from April 2022 to April 2023. The patients were randomly divided into Group A and Group B. The patients in Group A received remote ischemic treatment + arterial thrombolysis, whereas the patients in Group B received arterial thrombolysis. *Methods:* The coagulation indicators, inflammatory factors, quality of life, and adverse reactions of both groups were compared. *Results*: The blood coagulation indexes of the patients in Group A were better than those in Group B ($P < 0.05$); the inflammation indexes in Group A were lower than those in Group B ($P < 0.05$); the SF-36 scores in Group A were higher than those in Group B ($P < 0.05$); the adverse reaction rate in patients with cerebral infarction was lower than that in Group B ($P < 0.05$). *Conclusion*: Remote ischemic conditioning + arterial thrombolysis is effective and feasible in treating patients with ultra-early cerebral infarction, and it inhibits inflammation and improves coagulation function.

Keywords: Ultra-early cerebral infarction; Arterial thrombolysis; Remote ischemic treatment; Curative effect

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1. Introduction

Cerebral infarction is a cerebrovascular disease that can damage brain function. This disease is prevalent, complicated, and life-threatening. Cerebral infarction is more common among older people due to their weakened immunity, and it is difficult to treat. In addition, after cerebral infarction, the blood supply to the brain can be affected, leading to brain tissue necrosis, causing impaired brain function and residual cognitive, language, and physical impairments, thereby reducing patients' quality of life. Currently, arterial thrombolysis is the primary treatment method for cerebral infarction. The most commonly used drug is urokinase, which can improve the neurological function of patients. Ultra-early administration of urokinase aids in clearing occluded cerebral blood vessels, diminishing the infarct area, and fostering the restoration of cerebral nerve function [1].

However, the effect of arterial thrombolysis alone is limited, and it cannot reduce neuronal damage and avoid reperfusion injury in the infarcted area. In recent years, some scholars have suggested the incorporation of remote ischemic conditioning (RIC) into the treatment of cerebral infarction, which can stimulate the distal limbs through ischemia to increase the tolerance of brain tissue to ischemia, thereby protecting the cranial nerves and avoiding reperfusion damage of ischemic brain tissue [2]. In this study, 60 patients with ultra-early cerebral infarction admitted from April 2022 to April 2023 were used as samples to explore the effect of remote ischemic treatment and arterial thrombolysis.

2. Material and methods

2.1. Information

60 patients with ultra-early cerebral infarction were used as samples for this study, which was carried out from April 2022 to April 2023. There were no significant differences in the baseline data of both groups ($P > 0.05$), as shown in **Table 1**.

Table 1. Baseline data of patients with cerebral infarction

Group	Gender		Age (years)		Onset time (h)		Basic illness		
	Male	Female	Range	Average	Range	Average	Diabetes	Hypertension	Heart disease
Group A ($n = 30$)	18	12	52–88	69.11 ± 2.42	0.5–5	2.41 ± 0.36	10	12	8
Group B ($n = 30$)	19	11	52–89	69.13 ± 2.39	0.5–5.5	2.43 ± 0.38	11	13	6
χ^2/t	0.0705		0.0322		0.2093		0.0687		
P	0.7906		0.9744		0.8350		0.8012		

2.2. Inclusion and exclusion criteria

Inclusion criteria: (1) MRI suggested cerebral infarction, (2) onset time < 6 hours; (3) signed an informed consent, (4) first cerebral infarction.

Exclusion criteria: (1) Abnormal immune system, (2) abnormal visceral function, (3) drug allergy, (4) history of traumatic brain injury, (3) brain tumor.

2.3. Treatment methods

After the patients were enrolled in the study, various treatments were administered, including diuresis, dehydration, oxygen inhalation, management of hypoglycemia, hypotension, pH adjustment, water-electrolyte correction, and other relevant therapeutic measures. Simultaneously, supplementary measures such as brain neurotrophy, intracranial pressure adjustment, and reconstruction of brain microcirculation were implemented.

Group A underwent RIC in addition to arterial thrombolysis: The procedure involved the use of two non-invasive blood pressure cuffs. One cuff was placed around the upper limb, approximately 1–2 cm above the elbow joint, while the other was affixed to the lower limb, positioned approximately 3–5 cm above the lower joint. The cuffs were inflated to achieve a pressure of 200 mmHg to momentarily obstruct blood flow, resulting in the temporary absence of dorsal pedis artery and cerebral artery pulses. Once the desired pressure was reached, inflation ceased. Each treatment session consisted of maintaining inflation and pressure for 5 minutes, followed by a 5-minute deflation period. The process involved alternating inflation and pressure between the upper and lower limbs, completing three cycles of alternating pressurization during each session. This treatment regimen was administered once a day for a duration of 7 days.

Group B underwent arterial thrombolysis: Patients were positioned supine and administered anesthesia along with heparin. Subsequently, a No. 7 injection needle was utilized to puncture the pulsating area of the anterior carotid artery of the sternocleidomastoid, ensuring the needle tip was maintained at a 45° oblique puncture angle. The thrombolytic drug was administered at a rate of 2 mL/min through intra-arterial infusion. Following the completion of intra-arterial thrombolytic administration, angiographic examination was conducted to ensure vascular patency. The disappearance of local vascular occlusion was observed, and if occlusion persisted, an additional dose of urokinase (100,000 U) was administered, with a total dosage not exceeding 750,000 U. After the treatment was completed, the needle tube was removed, and gentle vertical pressure was applied to the local area for 15 minutes.

2.4. Observation indicators

(1) Coagulation: An automatic coagulation analyzer was used to detect indicators such as thrombin time (TT), prothrombin time (PT), activated partial thromboplastin time (APTT), and fibrinogen (FIB).

(2) Inflammation: Detection of tumor necrosis factor-α, interleukin-6, and hypersensitive-C-reactive protein indicators.

(3) Quality of life: The quality of life of the patients was assessed with a short-form survey (SF-36); the scores positively correlate with the quality of life of the patients.

(4) Adverse reactions: The incidence of adverse reactions including fatigue, upper gastrointestinal bleeding, gastrointestinal irritation, etc. were recorded.

2.5. Statistical analysis

Statistical analysis was completed using SPSS21.0, and categorical variables were expressed as percentages; measurement data were expressed as mean ± standard deviation. In comparing measurement data between two groups, the t-test was employed if the data met the typical assumptions; otherwise, the rank sum test was used. Differences in categorical variables were assessed using the chi-square test. A significance level of $P < 0.05$ was considered statistically significant.

3. Results

3.1. Blood coagulation indicators

After medication, the blood coagulation indexes of the patients in Group A were better than those in Group B ($P < 0.05$), as shown in **Table 2**.

Table 2. Analysis of blood coagulation indicators in patients with cerebral infarction (mean ± standard deviation)

Group	TT (s)		PT (s)		APTT (s)		FIB (g/L)	
	Before medication	After medication	Before medication	After medication	Before medication	After medication	Before medication	After medication
Group A (n = 30)	11.78 ± 1.25	15.01 ± 1.32	10.35 ± 2.11	15.01 ± 2.43	26.21 ± 1.35	30.67 ± 2.11	3.61 ± 0.45	4.68 ± 1.11
Group B (n = 30)	11.82 ± 1.27	12.84 ± 1.29	10.34 ± 2.09	11.24 ± 2.25	26.19 ± 1.34	27.45 ± 2.09	3.63 ± 0.49	3.82 ± 1.08
t	0.1229	6.4397	0.0184	6.2352	0.0576	5.9385	0.1647	3.0415
P	0.9026	0.0000	0.9853	0.0000	0.9543	0.0000	0.8698	0.0035

3.2. Inflammatory indicators

After medication, the inflammatory indicators in Group A were lower than in Group B ($P < 0.05$), as shown in **Table 3**.

Table 3. Inflammatory indicators of the patients (mean ± standard deviation)

Group	Tumor necrosis factor-α (μg/L)		Interleukin-6 (pg/mL)		Hypersensitive-C reactive protein (μmol/L)	
	Before medication	After medication	Before medication	After medication	Before medication	After medication
Group A ($n = 30$)	70.61 ± 2.88	36.11 ± 1.85	191.36 ± 4.51	100.36 ± 2.96	7.79 ± 1.36	4.25 ± 0.62
Group B ($n = 30$)	70.63 ± 2.91	43.69 ± 2.01	191.41 ± 4.49	155.61 ± 3.18	7.75 ± 1.41	5.43 ± 0.74
t	0.0268	15.1979	0.0430	69.6564	0.1118	6.6948
P	0.9787	0.0000	0.9658	0.0000	0.9113	0.0000

3.3. Quality-of-life indicators

After treatment, the scores of SF-36 in Group A were higher than those in Group B ($P < 0.05$), as shown in **Table 4**.

Table 4. Analysis table of SF-36 scoring indicators (mean ± standard deviation)

Group	Physical health (points)		Mental health (points)		Physiological functions (points)		Social functions (points)	
	Before medication	After medication	Before medication	After medication	Before medication	After medication	Before medication	After medication
Group A ($n = 30$)	62.58 ± 2.42	81.36 ± 3.29	63.11 ± 2.38	80.49 ± 3.35	62.48 ± 2.36	80.42 ± 2.88	60.36 ± 2.41	80.36 ± 2.91
Group B ($n = 30$)	62.61 ± 2.39	74.66 ± 2.78	63.13 ± 2.36	75.15 ± 2.84	62.51 ± 2.33	75.43 ± 2.75	60.39 ± 2.43	74.81 ± 2.86
t	0.0483	8.5199	0.0327	6.6597	0.0495	6.8636	0.0480	7.4503
P	0.9616	0.0000	0.9740	0.0000	0.9607	0.0000	0.9619	0.0000

3.4. Adverse reactions

The rate of adverse reactions of Group A was lower than that of Group B ($P < 0.05$), as shown in **Table 5**.

Table 5. Analysis table of cerebral infarction complications (mean ± standard deviation)

Group	Fatigue	Upper gastrointestinal bleeding	Gastrointestinal irritation	Incidence rate
Group A ($n = 30$)	0 (0.00)	0 (0.00)	1 (3.33)	3.33
Group B ($n = 30$)	1 (3.33)	2 (6.67)	3 (10.00)	20.00
χ^2	-	-	-	4.0431
P	-	-	-	0.0444

4. Discussion

Cerebral infarction is life-threatening, so it should be diagnosed and treated promptly.

When treating cerebral infarction diseases, comprehensive discussions should be undertaken regarding the treatment plan by considering factors such as the cause of the disease, symptoms, and medical history. The primary objectives should include restoring blood supply to the brain's ischemic site, reinstating brain microcirculation, enhancing brain cell function, preventing cerebral edema, and slowing the progression of cerebral infarction [3]. Conventional diuresis, dehydration, oxygen supply, regulation of intracranial pressure,

and improvement of microcirculation can alleviate the condition of cerebral infarction, but the overall curative effect is limited. Therefore, it is essential to explore effective treatment options for cerebral infarction to reduce its mortality rate [4]. In recent years, thrombolytic regimens have been gradually used to treat cerebral infarction, and many lives have been saved. However, studies have shown that thrombolysis at different time points following cerebral infarction yields diverse effects. Despite this variation, scholars generally agree that thrombolysis should be carried out at the ultra-early stage [5].

Thrombolytic therapy within 6 hours of cerebral infarction can promote the recovery of cranial nerve function and improve the safety of thrombolysis. The later the procedure is carried out, the higher the risk of secondary intracranial hemorrhage in patients, resulting in a poorer prognosis. The most commonly used thrombolytic drug is urokinase, which is safe. It can activate plasminogen and convert it into plasmin, thus avoiding cerebrovascular adverse events. Depending on the procedure, thrombolytic therapy can be divided into two types: intravenous thrombolysis and arterial thrombolysis, with the latter being relatively superior. Carotid artery thrombolysis stands as a standard clinical approach. Administering urokinase directly to the occluded vascular area does not affect blood coagulation indicators, ensuring high drug safety. While intravenous thrombolysis offers simplicity in operation, its treatment window is short, necessitating completion within 4 hours of onset. Moreover, intravenous thrombolysis requires a higher dose of urokinase, escalating the risk of side effects. Consequently, physicians often prefer recommending arterial thrombolysis for cerebral infarction patients [6]. Simple thrombolytic therapy can recanalize local blood vessels and alleviate the symptoms of cerebral infarction, but the complication rate of cerebral infarction remains high. Therefore, it is essential to explore safe and efficient solutions to improve the prognosis of patients with cerebral infarction [7]. The RIC scheme has been gradually used to treat cerebral infarction in the context of the continuous deepening medical research on cerebral infarction. Studies show that transient and constant insufficient blood oxygen supply stimulates the distal limbs during RIC treatment. This can enable the body's endogenous ischemic protection mechanism, strengthen the antioxidant defense system, and prevent free radicals from damaging the brain tissues [8]. Moreover, the RIC procedure is easy to perform, cost-effective, and non-invasive. The treatment solely involves using a non-invasive blood pressure cuff for compression therapy, making it a simple process to carry out.

The results of this study indicate that RIC + arterial thrombolysis can optimize blood coagulation indicators, inhibit the inflammatory response, and is safe and efficient. This is because alteplase can interact with plasminogen during arterial thrombolytic therapy but will not trigger a systemic fibrinolytic reaction. Besides, this regimen can improve the coagulation function of patients and inhibit the inflammatory response. This is because RIC involves increasing the local pressure of the limbs, creating a condition of reduced blood oxygen supply. This prompts the body to adapt to low oxygen levels, triggering internal protective mechanisms through hormonal and nerve regulation. These mechanisms mobilize natural defenses to prevent and manage ischemic damage in brain tissue [9]. However, the actual thrombolytic therapy should not be neglected. The half-life of alteplase is short, which can lead to neurological deterioration within a few hours after thrombolysis and increase the risk of secondary occlusion of blood vessels. Therefore, alteplase should be administered quickly, and the blood pressure changes in patients should be monitored, combined with expansion therapy if necessary [10].

5. Conclusion

In short, the RIC + arterial thrombolysis is effective in treating patients with ultra-early cerebral infarction. Besides, it enhances the coagulation function, improves the anti-inflammatory effect, and has fewer adverse effects compared to thrombolytic therapy alone. Therefore, this regimen should be promoted in clinical practice.

Disclosure statement

The authors declare no conflict of interest.

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