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Clinical Study of Acupuncture Combined with Alteplase and Tirofiban in the Treatment of Patients with Acute Ischemic Stroke

Zhen Liu[1*], Zhiyong Peng[2], Liandeng Xu[2] and Ping Zheng[2]

[1]Shenzhen Bao 'an District Hospital of Traditional Chinese Medicine, No.25, Yu' an Road, Shenzhen Bao'an District 30 District

[2]Emergency Department of Shenzhen Baoan District Hospital of Traditional Chinese Medicine, No.25, Yunan 2nd Road, 30 District, Baoan District, Shenzhen

Keywords

Acupuncture, Alteplase, Tirofiban, Acute ischemic stroke

***Correspondence**

Zhen Liu, Shenzhen Bao 'an District Hospital of Traditional Chinese Medicine, No.25, Yu' an Road, Shenzhen Bao'an District 30 District. E-mail: 357605951@qq.com

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Abstract

Background The clinical efficacy of acupuncture combined with alteplase and tirofiban in the treatment of patients with acute ischemic stroke (AIS) was investigated. **Methods** A total of 130 AIS patients who were treated in our hospital from February 2019 to February 2022 were selected and randomly divided into an observation group with 65 cases and a control group with 65 cases by random number table method. Patients in the control group were treated with conventional treatment and alteplase as well as tirofiban, while those in the observation group were additionally treated with acupuncture on the basis of the control group. The clinical efficacy, National Institute of Health Stoke Scale (NIHSS) and Mini-Mental State Examination (MMSE) scores, and the levels of inflammatory factors as well as vascular endothelial function indexes were compared between the two groups. **Results** After the treatment, the total effective rate in the observation group was obviously higher than that in the control group (P<0.05). The NIHSS score in the two groups was significantly lower while the MMSE score was evidently increased compared with those before the treatment. The change in the observation group was significantly greater than that in control group (P<0.05). After the treatment, the levels of hypersensitive C-reactive protein (hs-CRP), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) in both groups were distinctly lower than those before the treatment, and the levels in the observation group were evidently lower than those in the control group (P<0.05). Nitric oxide (NO) level in the two groups was obviously increased compared with that before the treatment while endothelin-1 (ET-1) level was remarkably decreased. The change in the observation group was evidently greater than that in the control group (P<0.05). In

addition, there were no adverse reactions in the two groups during the treatment. **Conclusion** Acupuncture combined with alteplase and tirofiban in the treatment of patients with AIS has a significant effect, which can ameliorate symptoms of neurologic impairment, vascular endothelial function and hemorheological status, improve the quality of daily life, and alleviate inflammation in patients. Moreover, it has favorable safety.

1 Introduction

Acute ischemic stroke (AIS), also known as acute cerebral infarction, is a common cerebrovascular disease. In AIS, the local blood supply disorder of the patient's brain causes ischemia and hypoxia of brain cells, leading to localized ischemic injury and neurological impairment of the brain[1]. At present, intravenous thrombolysis and interventional therapy are the main methods of Western medicine in the treatment of cerebral infarction. As a commonly used thrombolytic agent in clinic, alteplase (rt-PA) can selectively activate plasminogen and reduce bleeding complications, but the sequelae is obvious, which will seriously damage the fibrinolytic system of AIS patients[2]. Its clinical therapeutic effect is limited, which needs to be combined with the antiplatelet drug tirofiban to resist the secondary activation of platelets and prevent cardiac ischemic disease[3]. The long-term effect of the combination of the two is not obvious, and there are many adverse reactions in the long-term use of the drugs. According to traditional Chinese medicine, the main pathogenesis of cerebral infarction is the imbalance of Yin and Yang and the disorder of Qi and blood caused by deficiency of Qi and weakness in blood circulation in the body plus the disturbance of external pathogens or the injury of diet and emotion. Furthermore, "benefiting blood, activating blood circulation and removing blood stasis" are taken as the basic principle of treating cerebral infarction. Acupuncture is an important external treatment method in traditional Chinese medicine, which has the effects of balancing Yin and Yang, harmonizing Qi and blood, and dredging meridians and collaterals, and it has good curative effects on the clinical treatment of cerebral infarction[4]. Based on this, in the present study, it was combined with alteplase and tirofiban to explore the feasibility for its clinical application by comparing the clinical efficacy, National Institute of Health Stoke Scale (NIHSS) score, Mini-Mental State Examination (MMSE) score, inflammatory factor levels and vascular endothelial function index levels in the two groups. Now the results of the research are reported as follows.

2 Materials and methods

2.1 General data

A total of 130 AIS patients who were treated in our hospital from February 2019 to February 2022 were selected and randomly divided into an observation group (n=65) cases and a control group (n=65) by random number table method. There was no significant difference in general information, such as gender, age, admission time and complications (Multiple complications can occur simultaneously to one patient), between the two groups (P>0.05), as presented in Table 1.

Table 1 Comparison on general information of AIS patients between the two groups

Groups		Control group (n=65)	Observation group (n=65)	χ^2/t	P
Gender (cases)	Male	34	30	0.492	0.483
	Female	31	35		
Age (years old)		65.70±7.34	64.04±5.00	1.509	0.134
Admission time (years)		1.99±0.65	2.02±0.53	-0.277	0.782
Complications	Hypertension	40 (61.54)	41 (63.07)	0.033	0.856

[cases (%)]	Diabetes	14 (21.54)	12 (18.46)	0.192	0.661
	Coronary disease	20 (30.77)	24 (36.9)	0.550	0.458
	Hyperlipidemia	30 (46.15)	32 (49.23)	1.140	0.286

2.2 Inclusion criteria

① All patients met the diagnostic criteria of acute cerebral infarction[5]; ② All patients catching the disease for the first time; ③ The onset time in patients was no more than 48 h.

2.3 Exclusion criteria

① Patients with severe dysfunction of organs such as heart, liver and kidney; ② Patients who are allergic to the drugs in this study; ③ Patients with previous history of drug abuse, brain trauma or cerebral vascular intervention; ④ Patients with previous history of cephalagra, epilepsia or encephalitis; ⑤ Patients with hypertensive encephalopathy or brain lesions caused by poisoning or other reasons; ⑥ Patients with hemorrhage and transient cerebral ischemia; ⑦ Patients with blood system disease; ⑧ Those with needle sickness in the past.

2.4 Treatment methods

Patients in both groups were given conventional treatment, including respiratory support, ECG monitoring, anticoagulation, defibringen, intracranial decompression, anti-infection and nerve nutrition. Patients in the control group were given ateplase (specification: 20 mg/tube, Germany Boehringer-Ingelheim company, State Food And Drug Administration (SFDA) Approval No.: SJ20160054) at 0.9 mg/kg, and received tirofiban (specification: 5 mg, Hangzhou Zhongmei Huadong Pharmaceutical Co.,Ltd., SFDA Approval No.: H20060265) after thrombolytic treatment. During the administration, the vital signs of the patients were closely monitored. Among them, 10% of the 100 mL mixture of alteplase at 0.9 mg/kg and 0.9% sodium chloride solution was injected intravenously within 60 seconds (s), and the remaining (90%) was injected intravenously within 1 hour (h). Tirofiban was continuously pumped intravenously for 30 minutes (min) at 0.40 μg/(kg·min), and then continuously pumped intravenously for 72 h at 0.15 μg/(kg·min). The above treatment was performed once a week, and 4 weeks was a course of treatment.

Patients in the observation group were treated with acupuncture on the basis of the control group. Filiform needles of 0.20 mm × 40 mm were used. Acupoints including Dicang (ST4), Xiaguan (ST7), Jiache (ST6), Zusanli (ST36), lateral line 1/2 of vertex (MS8/9) and anterior/posterior oblique line of vertex-temporal (MS6/7) were selected. The skin at the target acupoints was routinely disinfected. The acupoints Dicang (ST4), Xiaguan (ST7) and Jiache (ST6) were subjected to reducing manipulations by lifting and inserting the needle. Zusanli (ST36) was treated using reinforcing manipulations by lifting and inserting the needle. Lateral line 1/2 of vertex (MS8/9) and anterior/posterior oblique line of vertex-temporal (MS6/7) were subjected to twirling reducing method. After the desired sensation was brought, hand-manipulating of needle was performed for 3 min, and then the needle was retained for 30 min. The above treatment was carried out once a week, and 4 weeks was a course of treatment.

2.5 Observational indexes

2.5.1 NIHSS and MMSE scores[6]

NIHSS and MMSE were used to score the neurological and cognitive functions of patients before the treatment and 1, 2 and 4 weeks after the treatment. NIHSS includes 11 indicators, such as consciousness level, gaze, visual field and upper and lower limb movement, with a total score of 42 points. The higher the score, the more severe the neurological damage and the worse the neurological function of patients. MMSE includes 7 indicators, namely orientation, immediate memory, language, attention, visual-spatial ability, capacity of calculation and delayed memory, with a total score of 30 points. The higher the score, the better the patient's neurological and cognitive functions.

2.6 Inflammatory factor levels 5 mL fasting peripheral venous blood was collected before and after the treatment, and the serum was separated. The levels of hypersensitive C-reactive protein (hs-CRP) (Article No.: mlE1119), tumor necrosis factor-α (TNF-α) (Article No.: mlE102) and interleukin-6 (IL-6) (Article No.: mlE131) were measured by enzyme-linked immunosorbent assay (ELISA). The above kits were purchased from Shanghai EK-Bioscience Biotechnology Co., Ltd. All operations were carried out in strict accordance with the kit instructions.

2.7 Vascular endothelial function[7] 5 mL fasting peripheral venous blood was collected before and after the treatment, and the levels of nitric oxide (NO) and endothelin-1 (ET-1) were detected by nitrate reductase method and radioimmunoassay respectively.

2.8 Clinical efficacy evaluation[7] Basically cured: NIHSS score decreased by no less than 90%, and the degree of disability is grade 0. Markedly improved: NIHSS score decreased by more than 45% and less than 90%, and the degree of disability is grade 1-3. Improved: NIHSS score decreased by more than 18% and no more than 45%, and the degree of disability is grade 1-3. Unchanged: NIHSS score increased by no more than 18%. Deteriorating: NIHSS score increased by more than 18%. Total effective rate= (recovered+effective+markedly effective) cases/total cases×100%.

2.9 Statistical methods The statistical analysis was performed using SPSS 20.0. The χ^2 test was used to compare the enumeration data. The measurement data were presented in mean ± standard deviation （$\bar{x}\pm s$）. Comparisons between two groups were performed using the independent sample *t*-test. The data with $P<0.05$ were considered to be statistically significant.

3 Results

3.1 Comparison of NIHSS and MMSE scores between the two groups Before the treatment, there was no significant difference in NIHSS and MMSE scores between the two groups ($P>0.05$). After the treatment, the NIHSS score in the two groups was evidently lower than that before the treatment, while the MMSE score was distinctly higher than that before the treatment, and the change in the observation group was obviously greater than that in the control group ($P<0.05$). The details are listed in Table 2.

Table 2 Comparison of NIHSS and MMSE scores between the two groups

Groups	Number of cases	NIHSS score		MMSE score	
		Before treatment	After treatment	Before treatment	After treatment
Control group	65	16.96±2.22	9.84±2.02*	11.85±1.23	21.28±2.28*
Observation group	65	16.62±2.12	7.42±1.49*	11.86±1.14	25.50±0.91*
t		0.896	7.778	0.299	-13.893
P		0.372	0.000	0.960	0.000

Note: Compared with before the treatment: *$P<0.05$

3.2 Comparison of inflammatory factor levels between the two groups Prior to the treatment, there was no significant difference in hs-CRP, TNF-α and IL-6 levels between the two groups ($P>0.05$). After the treatment, hs-CRP, TNF-α and IL-6 levels in both groups were obviously lower compared with those before the treatment, and the levels in the observation group were remarkably lower than those in the control group ($P<0.05$), as presented in Table 3.

3.3 Comparison of vascular endothelial function between the two groups Before the treatment, difference in the levels of NO and ET-1 between the two groups was not significant ($P>0.05$). After the

treatment, NO level in both groups was distinctly higher than that before the treatment, while the level of ET-1 was obviously down-regulated compared with that before the treatment, and the change in the observation group was significantly greater than that in the control group (P<0.05). The details are listed in Table 4.

3.4 Comparison of clinical efficacy between the two groups The total clinical effective rate in the observation group was significantly higher than that in the control group (P<0.05), as shown in Table 5.

Table 3 Comparison of hs-CRP, TNF-α and IL-6 levels between the two groups

Observational indexes		Control group (n=65)	Observation group (n=65)	t	P
hs-CRP (mg/mL)	Before treatment	16.37±2.64	16.55±2.78	-0.371	0.711
	After treatment	12.37±2.37*	7.01±1.65*	14.943	0.000
TNF-α (pg/mL)	Before treatment	26.40±1.86	26.26±1.39	0.490	0.625
	After treatment	25.37±1.55*	13.12±1.04*	52.935	0.000
IL-6 (pg/mL)	Before treatment	11.99±1.00	12.18±1.14	-0.681	0.497
	After treatment	7.45±0.47*	4.22±0.43*	40.706	0.000

Note: Compared with before the treatment: *P<0.05

Table 4 Comparison of vascular endothelial function between the two groups（ $\bar{x}$±s）

Groups	Number of cases	NO (umol/L)		ET-1 (ng/L)	
		Before treatment	After treatment	Before treatment	After treatment
Control group	65	37.14±3.47	45.27±2.86*	164.13±8.65	107.13±11.37*
Observation group	65	37.64±2.74	53.12±3.76*	163.87±9.65	91.26±10.99*
t		-0.891	-13.382	0.299	8.090
P		0.374	0.000	0.960	0.000

Note: Compared with before the treatment: *P<0.05

Table 5 Comparison of clinical efficacy between the two groups [cases (%)]

Indexes	Control group (n=65)	Observation group (n=65)	χ^2	P
Basically cured	10 (15.38)	16 (24.62)	-	-
Markedly improved	16 (24.62)	22 (33.85)	-	-
Improved	22 (33.85)	22 (33.85)	-	-
Unchanged	15 (23.08)	4 (6.15)	-	-
Deteriorating	2 (3.08)	1 (1.54)	-	-
Total efficiency	48 (73.85)	60 (92.31)	7.789	0.005

3.5 Adverse reactions There were no adverse reactions in both groups during the treatment.

4 Discussion

Acute cerebral infarction is a brain tissue infarction caused by cerebral artery occlusion, accompanied by the injury of neurons, astrocytes and oligodendrocytes after activation. In central nervous system, it is the most important vascular event causing death and disability in modern society[2]. The primary measures to save patients with cerebral infarction are to dredge the blocked blood vessels as soon as possible, minimize the infarct area, rebuild the blood circulation in the ischemic area, and repair the damage of ischemic penumbra reduction to the nervous system. Intravenous injection of recombinant tissue plasminogen activator (rt-PA) combined with tirofiban can dissolve fibrin in thrombus and dredge blocked blood vessels. It is the most effective drug treatment for acute cerebral infarction in Western medicine. However, the thrombolytic time window of this method is narrow, and patients were prone to complications such as bleeding, drug allergy and reocclusion. According to traditional Chinese medicine, stroke belongs to "apoplexia" and "apoplexy", and its attack is based on vital-Qi decline and stagnation of cerebral vessels. The basic pathogenesis is the imbalance of Yin and Yang and the disorder of Qi and blood. Therefore, the disease should be mainly treated by supplementing Qi, activating blood circulation and removing blood stasis[4]. Acupuncture, as the main treatment in Chinese surgery, has the effects of balancing Yin and Yang, harmonizing Qi and blood, and dredging the meridians. It is recommended to be used in combination with Western medicine for the treatment of acute cerebral infarction in *Chinese guidelines for the diagnosis and treatment of acute ischemic stroke with combined Chinese and Western medicine 2017*[8]. In traditional Chinese medicine, stroke in patients is mainly due to deficiency in origin and the effect of accumulated internal injury, wind, fire, phlegm, blood stasis and so on, resulting in the movement of channel Qi in the brain being affected. Clinical treatment with acupuncture can calm the nerves, restore consciousness and open orifices, and has a good protective effect on brain tissue and nerve cells. Acupuncture on lateral line 1/2 of vertex (MS8/9) and anterior/posterior oblique line of vertex-temporal (MS6/7) on the head can stimulate the nerve trunk around the brain and facilitate the recovery of coordination of the affected limbs. The results of this study showed that after the treatment, NIHSS score in the two groups was significantly lower than that before the treatment, while MMSE score was obviously higher than that before the treatment, and the change in the observation group was evidently greater compared with that in the control group. The total clinical effective rate in the observation group was distinctly higher than that in the control group. These findings suggested that acupuncture combined with alteplase and tirofiban can significantly ameliorate symptoms of neurologic impairment in AIS patients and improve the life quality of patients, and its curative effect is obviously better than that of single Western medicine.

After acute cerebral infarction, due to the interruption of blood supply, the energy of the corresponding brain tissue is exhausted, and neuronal apoptosis is induced, which triggers the immune response of the body, causing inflammatory cell infiltration. The interactions of inflammatory reaction, activation of glial cells in the central nervous system, infiltration of peripheral inflammatory cells and release of multiple inflammatory factors further aggravate the neurological damage of patients. A study reported that detecting the levels of inflammatory cytokines in patients with AIS has important clinical significance in judging the severity of AIS[9]. Research[10] suggested that acupuncture can interfere with inflammatory signaling pathways by inhibiting the activation and infiltration of inflammatory cells, regulating the expressions of inflammation-related cytokines, and balancing the effects of pro-inflammatory and anti-inflammatory factors. The results of this study presented that after the treatment, the levels of inflammatory factors in the serum of patients in both groups decreased significantly,

indicating that acupuncture combined with alteplase and tirofiban can reduce the inflammatory reaction in patients with AIS.

NO is a free radical with neurotoxicity, which can act on superoxide free radicals to form peroxynitrite or be oxidized into nitrite anion, and participate in lipid peroxidation damage. Excessive NO will have serious cytotoxic effects[11]. ET-1 is the strongest vasoconstrictive peptide in the body, which can regulate brain circulation, stimulate the release of excitatory amino acids, indirectly accelerate the death of nerve cells in the ischemic area, and lead to worse blood supply in the ischemic area[12]. After acute cerebral infarction, patients' oxidative stress response is enhanced, which damages vascular endothelial function, resulting in reduced NO secretion and increased ET-1 synthesis. The imbalance between the two levels can induce vasospasm and contraction, leading to aggravated ischemia and hypoxia in local brain tissue and microcirculation disorders[13]. Acupuncture can stimulate nerve trunk around the brain, promote blood circulation, and shorten the recanalization time of blood vessels. The selected acupoints Jiache (ST6) and Xiaguan (ST7) can dredge the meridians and collaterals, and regulate Qi and blood. Zusanli (ST36) can tonify middle-Jiao and Qi, clear and activate the channels and collaterals, strengthen body resistance and eliminate evil. In this way, Qi and blood are dredged, movement of joints is smoothed, body immunity is adjusted, and disease resistance is enhanced. The results of this study exhibited that after the treatment, NO level in both groups was increased significantly while ET-1 level was decreased obviously, and the change in the observation group was evidently greater than that in the control group. The results suggested that acupuncture combined with alteplase and tirofiban can significantly improve vascular endothelial function and hemorheological status in patients with AIS. In addition, there were no adverse reactions in the treatment of patients in the two groups, indicating that acupuncture combined with alteplase and tirofiban is safe.

In conclusion, acupuncture combined with alteplase and tirofiban is effective in the treatment of AIS patients, which can significantly ameliorate the symptoms of neurological impairment, enhance life quality of patients, reduce inflammatory reaction and improve vascular endothelial function and hemorheology, and has good safety.

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Not applicable.

Conflict of Interest

The authors declare no conflicts of interest.

Author contributions

Conceptualization, Z.L and Z.Y.P; Data curation, L.D.X; Formal analysis, P.Z; Methodology, Z.L; Writing-Original draft, Z.Y.P and L.D.X; Writing-review and editing, P.Z and Z.L; All authors have read and agreed to the published version of the manuscript.

Ethics Approval and Consent to Participate

The study was approved by the Medical Ethics Committee, and the patients were informed and consented.

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Availability of Data and Materials

The data presented in this study are available on request from the corresponding author.

Supplementary Material

Not applicable

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