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Original Article

Effects of acupuncture on clinical outcome and helper T cell distribution and abundance in patients with convalescent ischemic stroke

Lingli Jin[1], Caiyan Han[2]

[1]Department of Traditional Chinese Medicine, Wuhan University People's Hospital of Hanchuan Hospital (People Avenue Hospital District), Xiaogan, Hubei Province, China; [2]Department of Neurology, Wuhan University People's Hospital of Hanchuan Hospital (People Avenue Hospital District), Xiaogan, Hubei Province, China

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Abstract: Objective: To study the effects of acupuncture on clinical outcomes and helper T cell levels in patients with convalescent ischemic stroke. Methods: One hundred and thirty-six patients with cerebral ischemic stroke were selected for this prospective study. Patients in the control group were treated with routine therapy, and patients in the observation group were treated with acupuncture for 30 minutes once a day for 14 days plus the treatment of the control group. The clinical efficacy, cognitive function, T cell subsets distribution and inflammatory factors of patients in both groups were recorded before and after treatment. Results: Total effectiveness rate of the observation group was significantly higher than that of the control group ($P<0.05$). After treatment, $CD3^+$ cell percentage, $CD4^+$ cell percentage and $CD4^+$ cell percentage/$CD8^+$ cell percentage of patients in both groups were significantly increased ($P<0.05$), while $CD8^+$ cell percentage in both groups was significantly decreased ($P<0.05$). Compared to those in the control group, the overall response rate as well as $CD3^+$ cell percentage, $CD4^+$ cell percentage and $CD4^+/CD8^+$ of patients after treatment in the observation group were higher ($P<0.001$), while $CD8^+$ cell percentage was lower (all $P<0.001$). Moreover, the improvement in inflammatory factors as well as scores of Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) in observation group were better than those of the control group ($P<0.001$) respectively. Conclusion: Treatment of cerebral ischemic stroke by acupuncture can improve clinical outcome and cognitive function, which may be related to its regulation of immune response and reduction of inflammation in vivo.

Keywords: Acupuncture, cerebral ischemic stroke, clinical outcome, immunity, inflammatory factors

Introduction

Cerebral ischemic stroke (CIS) is a common critical illness, which accounts for 80% of all cerebrovascular diseases and has become a top cause of death in China [1, 2]. CIS mostly occurs in the elderly aged >60 years characterized by acute onset and critical illness [3]. Previous studies have shown that the body starts to develop an immune inflammatory response at the early stage of CIS. This response is beneficial to the clearance of necrotic tissues and plays a protective role in the brain after ischemic stroke. However, the release of a large amount of inflammatory factors can cause damage to brain tissue accompanied by a reduction in lymphocytes and atrophy of immune organs in the body, which is clinically called immunosuppression induced by stroke. The risk of infection is further increased by the release of inflammatory factors after immunosuppression [4]. The inflammatory response can aggravate nerve damage, which plays an important role in the development of CIS. Inflammation also contributes to ischemia or hypoxia of tissues, which can accelerate vascular endothelial injury and vascular remodeling [5]. In addition, inflammation can induce oxidative stress reaction in vivo, promoting thrombus formation and aggravating the injury of nerve function [6]. Therefore, a persistent inflammatory state during the recovery period is not conducive to the recovery of neurological function of patients, and the effective clearance of

inflammatory factors is an important factor affecting the recovery of patients [7]. With the development of modern technology, great progress has been made in early diagnosis and treatment, and the mortality rate of CIS is decreasing. However, the disease still has a high rate of disability and some patients will be left with lifelong physical disorders, which is also an important reason for the decrease of quality of life in patients with CIS after treatment [8, 9]. Early rehabilitation training is advocated at the convalescent stage for CIS patients, but the overall efficacy is suboptimal [10]. Previous studies have shown that acupuncture can regulate the immune function of the body, and clinical studies have found a curative effect of acupuncture in the treatment of rheumatic arthritis, asthma, hyperthyroidism, tumor and other diseases [11-14]. At present, no relevant literature has been reported about the effect of acupuncture on the recovery and immune function of CIS patients. Based on this, the aim of this study was to investigate the effects of acupuncture on clinical outcomes, inflammatory factors, and immune function in CIS patients.

Materials and methods

Clinical information

136 patients with CIS admitted from January 2018 to November 2020 in Department of Neurology to our hospital were selected for prospective study. The patients were divided into a control group (n=68) and observation group (n=68) randomly. Patients in the control group were treated with routine therapy, and the patients in the observation group were treated with acupuncture on the basis of the treatment of the control group. All patients or their family members signed the informed consent, and this study was approved by the Ethics Committee of our hospital.

Inclusion criteria: Patients who met the diagnostic criteria for CIS [15]. who were aged 18-76 years; who were initially diagnosed with CIS; who met an National Institutes of Health Stroke Scale (NIHSS) score of 5-15 at admission and who were at the convalescence stage (from 2 weeks to 6 months after the onset of CIS) [16].

Exclusion criteria: patients who could not tolerate acupuncture treatment; Patients having a history of craniocerebral trauma, epilepsy and cerebrovascular disease; Patients who could not cooperate with the cognitive function assessment; Patients with cardiopulmonary insufficiency; patients with malignancy and patients with psychiatric disorders affecting cognition.

Methods

Control group: Patients in both groups were treated according to the treatment plan for CIS at the convalescence stage in *"Chinese guidelines on the management of cerebral infarction with integrated traditional Chinese and Western medicine (2017)"* [15]. The treatment included continual monitoring of electrocardiographic (ECG) and vital signs, routine oxygen inhalation, and monitoring and control of blood pressure and blood glucose. Patients were given oral aspirin enteric-coated tablets (Bayer AG Co., Ltd., Germany) at a dose of 100 mg once a day for antiplatelet therapy and oral atorvastatin calcium tablets (Pfizer Pharmaceutical Co., Ltd., USA) at a dose of 20 mg once a day for lipid lowering therapy. Also, 30 mg edaravone (National Medicines Pharmaceutical Co., Ltd., China) injection was added to 100 mL normal saline and was administered by intravenous drip twice a day for oxygen radical scavenging therapy.

Observation group: Patients with CIS at the convalescence stage were treated with acupuncture in addition to the treatment of the control group. The following acupoints were punctured with a 1.5-gauge needle with the uniform reinforcing-reducing method in all patients: Baihui, Shenting, Sishencong, Sanyinjiao, Zusanli, Neiguan, Shenmen. The treatment was given for 30 min each time for 14 days.

Outcome measures

Clinical efficacy was evaluated according to NIHSS 1 month after the intervention of acupuncture and was divided into cured, excellent, progress, and invalid [16]. The efficacy was determined according to the degree of decline in neurological deficit score. A reduction of 91-100% was determined as cure, 46-90% determined as excellent, 18-45% determined as progress and ≤17% determined as invalid. The total effective rate = (cure + excellent + progress)/total number of cases ×100%.

Table 1. Comparison of general information and baseline data between the two groups ($n/\bar{x} \pm sd$)

Item	Observation group (n=68)	Control group (n=68)	χ^2/t	P
Sex (male/female)	42/26	39/29	0.275	0.600
Age (years)	66.5±7.5	67.9±8.3	1.032	0.304
Education (years)	11.26±4.79	11.67±3.95	0.545	0.587
BMI (kg/m^2)	23.74±3.79	23.51±4.05	0.342	0.733
Time from onset to the beginning of intervention (d)	15.85±1.62	15.94±1.86	0.301	0.764
Stroke site			0.399	0.940
Brainstem	6	5		
Brain lobe	14	15		
Cerebellum	8	10		
Basal ganglia	40	38		
Comorbidities				
Hyperlipidemia			0.121	0.727
Yes	39	41		
No	29	27		
Hypertension			0.123	0.726
Yes	40	42		
No	28	26		
Coronary heart disease			0.131	0.717
Yes	22	24		
No	46	44		
Obesity			0.037	0.847
Yes	19	18		
No	49	50		
Hyperhomocysteinemia			0.151	0.697
Yes	49	51		
No	19	17		
Hyperuricemia			0.127	0.722
Yes	44	42		
No	24	26		

Note: BMI: body mass index.

The cognitive function of patients before therapy and 1 month after treatment in the two groups was assessed using the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). The total scores on the MMSE and MoCA are both 30 points, and a lower score indicated a worse cognitive function [15].

Detection of Tr cells and inflammatory factors in peripheral blood: 5 mL of venous blood was collected in the early morning from each CIS patient at the convalescence stage within 24 hours before acupuncture intervention and 14 days after treatment. The expressions of FITC-labeled anti-human CD3, CD4, and CD8 monoclonal antibodies were detected by FACSCanto II flow cytometer (BD Biosciences, USA), and $CD3^+$ cell percentage, $CD4^+$ cell percentage, $CD8^+$ cell percentage and $CD4^+$ cell percentage/$CD8^+$ cell percentage were compared.

The serum and plasma were separated by centrifuge (Shanghai Jumu Medical Optical Instruments Co., Ltd., China) at a speed of 3300 rpm for 15 min. Then 40 μL phosphate-buffered saline (PBS) buffer containing protease inhibitors (Xiamen Haibiao Technology Co., Ltd., China) was added to the isolated plasma and stored at -80°C. The levels of interleukin-6 (IL-6), C-reactive protein (CRP) and tumor necrosis factor-α (TNF-α) were measured by automatic

Table 2. Comparison of clinical efficacy between the two groups (n, %)

Group	Cure	Excellent	Progress	Invalid	Overall response rate (%)
Observation group (n=68)	6 (8.23)	38 (55.88)	20 (29.41)	4 (5.88)	62 (91.18)
Control group (n=68)	2 (2.94)	20 (29.41)	29 (42.65)	17 (25.00)	51 (75.00)
χ^2			17.278		6.332
P			0.001		0.012

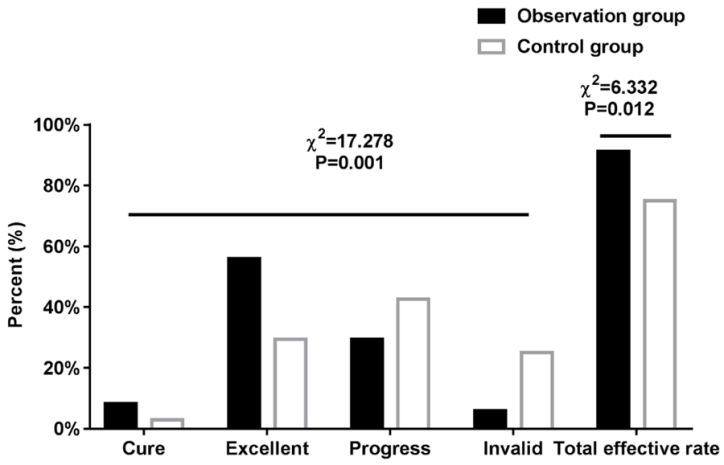

Figure 1. Comparison of clinical efficacy between the two groups.

multifunctional microplate reader (Thermo Fisher Scientific Inc, USA) and enzyme-linked immunosorbent assay (ELISA, Shanghai Biorui Biotechnology Co., Ltd., China).

Statistical analysis

SPSS statistics 17.0 software was used for statistical analysis. Continuous variables with normal distribution and homogeneity of variance were expressed as means ± standard deviation ($\bar{x}$ ± sd). Independent sample t-test was used for comparison between groups, while intra-group comparisons were analyzed by paired-sample t-test. Enumerated data were expressed as number (n) or percentage (%) and analyzed using the Pearson chi-square test. P< 0.05 was considered significant.

Results

Comparison of general information

There were no significant differences in sex, age, education, BMI, time from onset to admission, stroke site, or comorbidities between the two groups (P>0.05). See **Table 1**.

Comparison of clinical efficacy between the two groups

Overall response rate in the observation group was higher than that in the control group (91.18% vs. 75.00%, P<0.05), as shown in **Table 2** and **Figure 1**.

Comparison of MMSE and MoCA scores between two groups before and after treatment

The MMSE and MoCA in the observation group were significantly improved after treatment (P< 0.05) and were better than those of the control group (P<0.001). See **Table 3**.

Comparison of Tr cell subsets in peripheral blood before and after treatment between the two groups

There was no significant difference in $CD3^+$ cell percentage, $CD4^+$ cell percentage, $CD8^+$ cell percentage or $CD4^+$ cell percentage/$CD8^+$ cell percentage before treatment (P>0.05). After treatment, $CD3^+$ cell percentage, $CD4^+$ cell percentage and $CD4^+$ cell percentage/$CD8^+$ cell percentage were significantly increased, while $CD8^+$ cell percentage was significantly decreased (P<0.05). Compared to those in the control group, $CD3^+$ cell percentage, $CD4^+$ cell percentage and $CD4^+$ cell percentage/$CD8^+$ cell percentage after treatment in the observation group were significantly higher, while $CD8^+$ cell percentage was lower (P<0.001). See **Table 4** and **Figure 2**.

Comparison of inflammatory factors before and after treatment between the two groups

After treatment, the levels of CRP, TNF-α, and IL-6 in the two groups were lower than those before treatment (P<0.05), and the degree of decrease in the observation group was greater

Table 3. Comparison of cognitive score before and after treatment between the two groups ($\bar{x} \pm s$)

Item	Before treatment		After treatment	
	Observation group (n=68)	Control group (n=68)	Observation group (n=68)	Control group (n=68)
MMSE (scores)	25.53±1.26	25.43±1.21	27.85±0.95$^{**,\#\#\#}$	25.76±1.84
MoCA (scores)	22.49±1.98	22.28±2.35	23.74±2.08$^{*,\#\#\#}$	22.29±2.15

Note: Compared with before treatment in the same group, $^{*}P<0.05$, $^{**}P<0.01$; compared with the control group after treatment, $^{\#\#\#}P<0.001$. MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment.

Table 4. Comparison of Tr cell subsets in peripheral blood before and after treatment between the two groups ($\bar{x} \pm s$)

Item	Before treatment		t	P	After treatment		t	P
	Observation group (n=68)	Control group (n=68)			Observation group (n=68)	Control group (n=68)		
$CD3^+$ cell percentage	55.32±9.87	55.76±10.02	0.258	0.797	64.74±8.67*	59.47±8.78*	3.522	<0.001
$CD4^+$ cell percentage	31.79±6.25	31.61±6.18	0.169	0.866	39.47±7.89*	34.87±7.19*	3.554	<0.001
$CD8^+$ cell percentage	23.75±2.41	23.79±2.64	0.092	0.927	21.51±1.86*	22.98±1.71*	4.798	<0.001
$CD4^+$ cell percentage/$CD8^+$ cell percentage	1.34±0.32	1.33±0.31	0.179	0.585	1.83±0.41*	1.54±0.39*	4.226	<0.001

Note: Compared with before treatment in the same group, $^{*}P<0.05$.

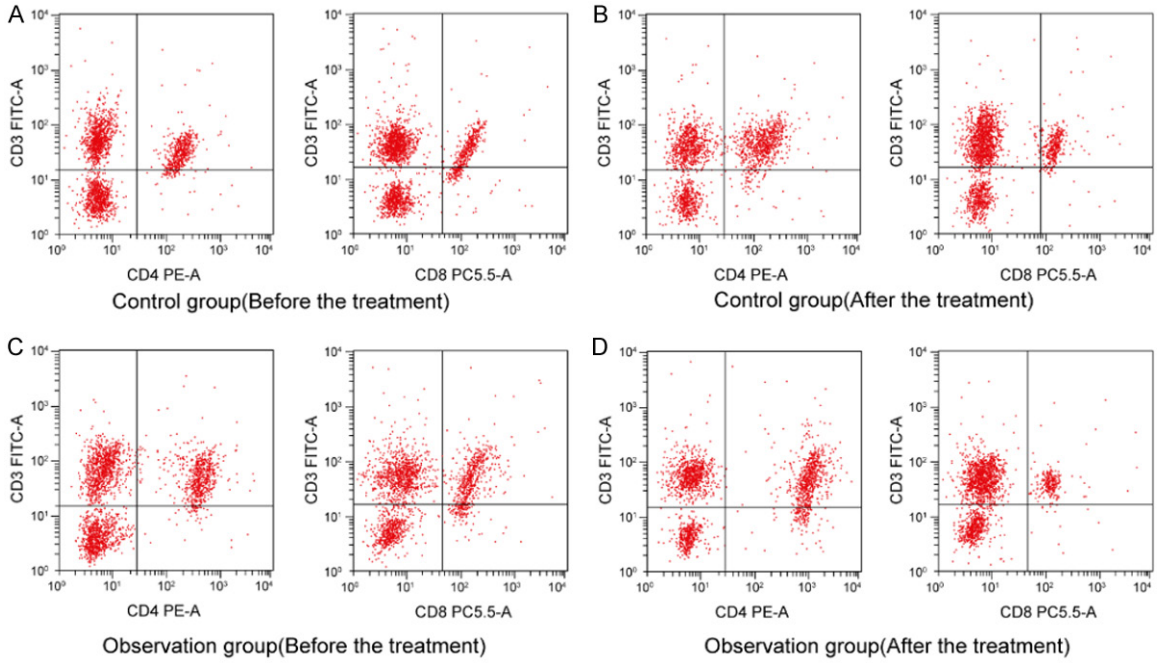

Figure 2. Comparison of CD3, CD4, and CD8 flow plots in the two groups before and after treatment. A: Control group (before treatment); B: Control group (after treatment); C: Observation group (before treatment); D: Observation group (after treatment).

than that in the control group (P<0.001). See **Table 5**.

Discussion

The pathophysiology of CIS is mainly due to oxidative stress in the body, which produces a large number of inflammatory factors and can lead to changes in hemodynamics, impaired blood flow, and injury of nerve cells [17]. The apoptosis of nerve cells can induce an immune response in vivo that can further aggravate the injury of nerve cells and lead to a vicious cycle [18]. CIS belongs to the category of stroke in

Table 5. Comparison of inflammatory factors before and after treatment between the two groups ($\bar{x}$ ± sd)

Item	Before treatment		After treatment	
	Observation group (n=68)	Control group (n=68)	Observation group (n=68)	Control group (n=68)
CRP (mg/L)	6.87±1.79	6.79±1.75	4.81±1.53$^{**,\#\#\#}$	5.71±1.52*
TNF-α (μg/mL)	123.98±18.71	124.06±18.84	87.01±15.03$^{***,\#\#\#}$	104.26±16.69***
IL-6 (μg/mL)	351.98±36.98	352.74±37.48	275.43±26.96$^{***,\#\#\#}$	318.97±31.52***

Note: Compared with before treatment in the same group, *P<0.05, **P<0.01, ***P<0.001; compared with the control group after treatment, $^{\#\#\#}$P<0.001.

Traditional Chinese Medicine (TCM), and acupuncture has a long history in the treatment of stroke. Studies have shown that acupuncture can leave the cortex and corticospinal tract of the brain in an excitable state and increase the excitability of motor nerves in the neural reflex circuit after stimulation of the Baihui acupoint, which can reduce muscle tone and promote nerve repair to enhance functional motor recovery [19]. A study in China found that, with the acupuncture therapy at the Du meridian and acupoints that promote blood circulation for removing obstruction in collaterals, stimulation of the cerebral cortex motor center can increase the blood supply of ischemic brain tissue and promote the repair of nerve function in CIS patients. This would improve the motor function and quality of daily life [20]. Another study showed that acupuncture could establish new neural circuits while promoting neuronal excitation [21]. Clinical studies have found that CIS can lead to cognitive impairment of patients after its occurrence. In this study, we found that acupuncture therapy combined with basic treatment was highly effective in CIS patients and improved the cognitive function, which may be related to acupuncture for promoting nerve repair.

Previous studies have shown that CIS can induce immunosuppression, and the release of inflammatory factors after immunosuppression increases the risk of infection [4]. Acupuncture has unique advantages in the prevention and treatment of immune diseases with significant effectiveness [14]. Some studies have shown that acupuncture may regulate the phagocytosis of macrophages and promote the secretion of immune factors to enhance the immunity of the organism. Moreover, acupuncture also has a regulatory effect on the key cellular mechanisms of central diseases [22, 23]. Acupuncture can activate microglia, which is an important part of the central immune response [24]. The main role of microglial activation in the body is to promote the production of neurotrophic factors, and it also regulates inflammatory factors and inhibits the oxidative stress reaction at the same time [25]. Acupuncture treats degenerative, central and inflammatory diseases primarily by regulating the activation of microglia in the body [26]. In recent years, acupuncture was proven able to regulate immune factors to control immune diseases [27]. Acupuncture also can increase the expression of immune T cells and promote the transformation of T lymphocyte [28]. Furthermore, acupuncture has a bidirectional regulation effect on the antibodies produced by B cells [29]. The current study showed that acupuncture could regulate the immune function of patients, which may be related to above-mentioned mechanisms.

Oxidative stress state, massive release of inflammatory cytokines in the brain, and endothelial dysfunction after cerebral vascular endothelial injury are all associated with the occurrence and development of cerebral infarction [30, 31]. Acupuncture reduces the levels of inflammatory factors in patients with CIS [32]. Another study suggested that electro-acupuncture may inhibit inflammatory factors by inhibiting the release of TNF-α by macrophages [33]. Acupuncture can effectively regulate NF-κB signaling pathway and reduce neuronal apoptosis to achieve anti-inflammatory effects [34]. In this study, the levels of inflammatory factors in patients treated with acupuncture were significantly decreased, which is consistent with the above research.

However, this study has limitations of small sample size and short duration of follow-up. Moreover, multi-point observation of improve-

ment of patients' conditions and evaluation of effect of acupuncture manipulations and acupoints on the clinical efficacy of CIS were not performed in the present study. Therefore, the mechanism by which acupuncture is effective in CIS patients remains to be further studied.

In conclusion, acupuncture therapy can improve clinical efficacy and cognitive function of patients with CIS, which may be related to its regulation of immune response and reduction of inflammation in vivo.

Disclosure of conflict of interest

None.

Address correspondence to: Caiyan Han, Department of Neurology, Wuhan University People's Hospital of Hanchuan Hospital (People Avenue Hospital District), No. 1 Renmin Avenue, Xiaogan 431600, Hubei Province, China. Tel: +86-13995871242; E-mail: hcy000927@163.com

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