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# Effect of acupuncture combined with drug therapy on the nerve cytokine secretion and oxidative stress in convalescence of cerebral infarction

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ABSTRACT

**Objective:** To explore the effect of acupuncture combined with drug therapy on the nerve cytokine secretion and oxidative stress in convalescence of cerebral infarction. **Methods:** A total of 118 patients in convalescence of cerebral infarction who were treated in the affiliated hospital of our school between August 2014 and December 2016 were divided into control group ($n$=59) and observation group ($n$=59) according to the random number table method. Control group received routine drug therapy, and the observation group received acupuncture combined with drug therapy. The differences in serum levels of neurotrophic factors, nerve injury factors and oxidative stress indexes were compared between the two groups before and after treatment. **Results:** The differences in serum levels of neurotrophic factors, nerve injury factors and oxidative stress indexes were not statistically significant between the two groups before treatment. After treatment, serum neurotrophic factors IGF-1, BDNF and NGF levels of observation group were higher than those of control group; nerve injury factors S-100 β , NSE, GFAP and UCH-L1 levels were lower than those of control group; oxidative stress indexes MDA, AOPPs and LHP levels were lower than those of control group while SOD and GSH-Px levels were higher than those of control group. **Conclusion:** Acupuncture combined with drug therapy can effectively optimize the nerve function, reduce the nerve injury and suppress the systemic oxidative stress response of patients in convalescence of cerebral infarction.

## 1. Introduction

Cerebral infarction is the cerebrovascular disease with highest incidence in the middle-aged and elderly, emergency thrombolytic therapy can be carried out within the time window after onset, and active anticoagulant therapy should be done if it is beyond the time window so as to avoid further embolism of target blood vessels and the ischemic hypoxic death of nerve cells[1,2]. After the positive acute phase treatment, the patients enter the rehabilitation period, but most patients still have different degrees of limb, language, cognition and other obstacles, and still need corresponding treatment[3,4]. Antiplatelet, nerve nutrition, regulating blood lipid and so on are all conventional therapies for patients in convalescence of cerebral infarction, but many current cases have shown that the effect of drug therapy alone is limited in optimizing the remaining dysfunction in patients with cerebral infarction, so some scholars recommend traditional Chinese medicine therapies such as acupuncture. As traditional Chinese medicine, acupuncture and moxibustion is with independent theory and method in the late conditioning of disease, and based on the concept "No obstruction, no pain" of traditional Chinese medicine, the target acupoint was punctured to attain the goal of treatment[5,6]. In this study, acupuncture was added in the overall treatment of patients in convalescence of cerebral infarction, and its application value was discussed from the nerve cytokine secretion, oxidative stress and other aspects, now reported as follows.

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## 2. Information and methods

### *2.1 Case information*

A total of 118 patients in convalescence of cerebral infarction who were treated in the affiliated hospital of our school between August 2014 and December 2016 were selected, and the families of the

patients were informed of the study process and signed informed consent. The enrolled patients were divided into the control group and the observation group by random number table, 59 cases in each group. Control group included 32 men and 27 women that were 48-76 years old; observation group included 30 men and 29 women that were 46-78 years old. In terms of gender and age distribution, the differences between the two groups were not significant ($P$>0.05), the subsequent study data were comparable, and the hospital ethics committee approved the study.

### 2.2 Inclusion and exclusion criteria

Inclusion criteria: (1) diagnosed with cerebral infarction for the first time; (2) having completed the acute phase treatment and were in rehabilitation period; (3) receiving no acupuncture treatment before; (4) cooperating with the whole treatment and related inspection, and with complete data. Exclusion criteria: (1) with history of cerebral hemorrhage and craniocerebral trauma; (2) combined with infectious diseases in other tissue organs; (3) combined with hyperthyroidism, pheochromocytoma and other diseases that caused the body to be in the state of stress and high consumption; (4) combined with malignant tumor diseases.

### 2.3 Therapy

Control group received conventional drug therapy for convalescence of cerebral infarction, including lowering blood pressure, lowering glucose, regulating lipid, protecting blood vessels, nourishing nerves, etc.

Observation group, based on conventional drug therapy, received acupuncture treatment, specifically as follows: the Jianyu, Quchi, Hegu, Shousanli and other acupoints of the affected-side upper extremities as well as the Zusanli, Yanglingquan, Liangqiu, Fenglong, Sanyinjiao, Taixi, Taichong and other acupoints of affected-side lower extremities were selected, mild reinforcing-reducing method was adopted, needle was retained for 20 min and twirled once every 5 min, and the treatment was conducted 2 times per week and lasted for 4 weeks in a row. The drug therapy was the same as that of control group.

### 2.4 Observation indexes

Before and after treatment, 5 mL of 6:00 am-8:00 am fasting cubital venous blood was collected from the two groups of patients, put in heparin anticoagulant sterile EP tube, and centrifuged at low speed to get the upper serum, which was stored in the cryogenic environment. Double-antibody sandwich solid-phase enzyme-linked immunosorbent assay (ELISA) was used to determine serum levels of neurotrophic factors, including insulin-like growth factor-1 (IGF-1), brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF); ELISA was used to determine the serum levels of nerve injury factors, including S-100β, neuron-specific enolase (NSE), glial fibrillary acidic protein (GFAP) and ubiquitin carboxyl-terminal hydrolase-1 (UCH-L1). ELISA was used to determine the serum levels of oxidative stress indexes, including the malondialdehyde (MDA), advanced oxidation protein products (AOPPs), lipid hydroperoxide (LHP), superoxide dismutase (SOD) AND glutathione peroxidase (GSH-Px).

### 2.5 Statistical processing

Statistical software was SPSS 25.0. Neurotrophic factors, nerve injury factors and oxidative stress indexes were in terms of mean ± standard deviation, comparison within same group between before and after treatment was by paired t test and comparison between two groups before treatment and after treatment was by grouping t test. Statistic $P$<0.05 was the standard of statistical significance in differences.

## 3. Results

### 3.1 Neurotrophic factors

Before treatment and 4 weeks after treatment, comparison of serum neurotrophic factors IGF-1 (μg/L), BDNF (ng/mL) and NGF (pg/mL) levels between two groups of patients was as follows: before treatment, serum IGF-1, BDNF and NGF levels were not significantly different between the two groups; serum IGF-1, BDNF and NGF levels of both groups of patients after treatment were significantly higher than those before treatment, and serum IGF-1, BDNF and NGF levels of observation group after treatment were higher than those of control group.

Table 1.
Changes in serum IGF-1, BDNF and NGF levels before and after treatment.

| Groups | $n$ | Time | IGF-1 | BDNF | NGF |
|---|---|---|---|---|---|
| Control group | 59 | Before treatment | 84.29±9.71 | 2.84±0.36 | 109.72±13.51 |
| | | After treatment | 91.63±10.85$^{*}$ | 3.71±0.48$^{*}$ | 117.83±14.69$^{*}$ |
| Observation group | 59 | Before treatment | 84.73±9.65 | 2.83±0.35 | 109.68±13.47 |
| | | After treatment | 115.82±14.79$^{*\#}$ | 4.92±0.57$^{*\#}$ | 145.62±17.39$^{*\#}$ |

Note: comparison of indexes within group between before and after treatment, $^{*}P$<0.05; comparison of indexes between observation group and control group after treatment, $^{\#}P$<0.05.

Table 2.
Changes in serum S-100 β , NSE, GFAP and UCH-L1 levels before and after treatment.

| Groups | *n* | Time | S-100 β | NSE | GFAP | UCH-L1 |
|---|---|---|---|---|---|---|
| Control group | 59 | Before treatment | 2.16±0.28 | 27.38±3.51 | 39.46±4.52 | 0.73±0.09 |
| | | After treatment | 1.72±0.25* | 20.62±2.75* | 30.78±4.37* | 0.51±0.07* |
| Observation group | 59 | Before treatment | 2.13±0.25 | 27.29±3.42 | 39.51±4.47 | 0.75±0.08 |
| | | After treatment | 1.18±0.16*# | 11.38±1.74*# | 21.63±2.74*# | 0.27±0.04*# |

Note: comparison of indexes within group between before and after treatment, $^{*}P<0.05$; comparison of indexes between observation group and control group after treatment, $^{\#}P<0.05$.

Table 3.
Changes in serum MDA, AOPPs, LHP, SOD and GSH-Px levels before and after treatment.

| Groups | *n* | Time | MDA | AOPPs | LHP | SOD | GSH-Px |
|---|---|---|---|---|---|---|---|
| Control group | 59 | Before treatment | 6.82±0.71 | 5.47±0.68 | 542.92±61.07 | 103.27±14.85 | 42.17±5.84 |
| | | After treatment | 5.17±0.59* | 3.82±0.41* | 392.16±45.27* | 138.16±15.09* | 54.83±6.51* |
| Observation group | 59 | Before treatment | 6.85±0.76 | 5.43±0.64 | 538.76±59.83 | 102.69±15.27 | 42.36±5.79 |
| | | After treatment | 3.09±0.35*# | 2.17±0.28*# | 217.53±26.79*# | 171.84±19.63*# | 71.79±2.85*# |

Note: comparison of indexes within group between before and after treatment, $^{*}P<0.05$; comparison of indexes between observation group and control group after treatment, $^{\#}P<0.05$.

### *3.2 Nerve injury factors*

Before treatment and 4 weeks after treatment, comparison of serum nerve injury factors S-100 β (μg/L), NSE (μg/L), GFAP (pg/L) and UCH-L1 (μg/L) levels between two groups of patients was as follows: before treatment, serum S-100 β , NSE, GFAP, UCH-L1 levels were not significantly different between the two groups; serum S-100 β , NSE, GFAP and UCH-L1 levels of both groups of patients after treatment were significantly lower than those before treatment, serum S-100 β , NSE, GFAP and UCH-L1 levels of observation group after treatment were lower than those of control group.

### *3.3 Oxidative stress indexes*

Before treatment and 4 weeks after treatment, comparison of serum oxidative stress indexes MDA (μmol/L), AOPPs (μmol/L), LHP (μmol/L), SOD (U/L) and GSH-Px (ng/L) levels between two groups of patients was as follows: before treatment, serum MDA, AOPPs, LHP, SOD and GSH-Px levels were not significantly different between the two groups; serum MDA, AOPPs and LHP levels of both groups of patients after treatment were significantly lower than those before treatment while SOD and GSH-Px levels were significantly higher than those before treatment, and serum MDA, AOPPs and LHP levels of observation group after treatment were lower than those of control group while SOD and GSH-Px levels were higher than those of control group.

## 4. Discussion

As the blood vessels are not fully recanalized or the damaged nerve cells are not fully recovered, the patients in convalescence of cerebral infarction are mostly with different degree of limb function, language and mental disorders, so they need continuous treatment to optimize the illness[7,8]. Based on the causes of cerebral infarction, antiplatelet, regulating lipid, lowering glucose, lowering blood pressure and so on are all the basic therapies for rehabilitation period, but the effect of drug therapy is limited, and some patients still have serious lifetime functional defects. Acupuncture is a common auxiliary therapy for convalescence of cerebral infarction, which punctures the target acupoints of affected-side limbs to regulate qi-blood circulation and dredge the blocked meridian, eventually reduce cerebrovascular tensity, improve brain blood supply shortage and hypoxia, optimize the nerve cell function in lesions, and thus fundamentally reduce the dysfunction in areas dominated by damaged nerves[9,10]. In this study, acupuncture was introduced in the treatment of patients in convalescence of cerebral infarction, and its role in the rehabilitation of patients was clarified from the level of serum indexes.

The core cause of nerve injury caused by cerebral infarction is the ischemia hypoxia in the area with infarction, which leads to the apoptosis of neurons and the dysfunction of the dominated region. Normal operation of nerve cell function depends on the support of many neurotrophic factors, the secretion of corresponding neurotrophic factors declines after neuron damage happens, which cannot effectively resist the ischemic hypoxic damage, and eventually leads to irreversible apoptosis of neurons[11]. IGF-1, BDNF and NGF are the neurotrophic factors reported in different studies, IGF-1 inhibits the neurotransmitter release, increases cerebral blood flow and inhibits neuronal apoptosis, BDNF helps maintain the neuron survival, growth, differentiation and repair after injury[11], and NGF regulates the growth and development of peripheral and central neurons, and maintains neuron survival[12]. In the study, the differences in serum levels of these neurotrophic factors were compared between two groups of patients, and it was found that compared with those before treatment, serum IGF-1, BDNF and NGF levels of both groups of patients increased after treatment, showing that both therapies are effective; further compared with those of control group, serum IGF-1, BDNF and NGF levels of observation group of patients were higher after treatment, confirming that the acupuncture combined with drug therapy can be more effective to increase neurotrophic factor release and promote neuron repair.

Nerve injury factors are contrary to neurotrophic factors, they are massively released early after cerebral infarction, and their levels are highly consistent with the degree of nerve damage. S-100 β and NSE are the most commonly reported nerve injury factors in clinical practice, S-100 β and NSE go out of the cells through the damaged nerve cell membrane after local cerebral ischemia hypoxia,

and they further enter and are detected in the peripheral blood through the blood brain barrier whose permeability changes[13,14]. GFAP and UCH-L1 can also reflect the nerve injury severity, they are specifically expressed in neurons in physiological state, the composition is stable in the cerebrospinal fluid and peripheral blood, so they are easy to be detected, and studies have confirmed that its sensitivity for the diagnosis of cerebral infarction is more than 70%[15,16]. In this study, the differences in serum levels of these nerve injury markers were compared between two groups of patients, and it was found that compared with those before treatment, serum S-100β, NSE, GFAP and UCH-L1 levels of both groups of patients decreased after treatment, showing that both therapies can alleviate nerve injury degree; further compared with those of control group, serum S-100β, NSE, GFAP and UCH-L1 levels of observation group of patients were lower after treatment, confirming that the acupuncture combined with drug therapy can more effectively inhibit nerve damage progress and effectively protect the neuron function.

The existence of persistent oxidative stress is an important cause of cerebral infarction, and also involved in neuronal ischemic hypoxic injury. After cerebral infarction, a large number of oxygen free radicals are released, and the synthesis of oxidative metabolites MDA, AOPPs, LHP and others increases, which leads to the further dysfunction of the damaged neurons[17,18]. In the early damage, the body can increase the reactive release of SOD, GSH-Px and other antioxidants to neutralize oxidation products and inhibit oxidative stress response, but with the progress of cerebral infarction, the protective feedback function is weakened, and the antioxidants are massively consumed and at low levels[19-21]. Oxidation/antioxidant substance content can objectively reflect the level of oxidative stress and brain injury, and it was found in the study that compared with those before treatment, serum MDA, AOPPs and LHP levels of both groups of patients decreased while SOD and GSH-Px levels increased after treatment, showing that both therapies can suppress the oxidative stress reaction; further compared with those of control group, serum MDA, AOPPs and LHP levels of observation group of patients were lower while SOD and GSH-Px levels were higher after treatment, confirming that the acupuncture combined with drug therapy can more effectively inhibit systemic oxidative stress response, and this is also one of the specific mechanisms for it to protect the brain and optimize the neural function.

At the same time of basic drug therapy, the combined acupuncture therapy for patients in convalescence of cerebral infarction can nourish the nerves, reduce nerve injury, inhibit systemic oxidative stress and so on so as to ultimately protect the brain and promote rehabilitation, and it is an ideal combination therapy and worthy of popularization and application in clinical practice in the future.

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