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Original Research Article

Efficacy of a combination of Yiqi Huoxue Tongluo decoction and Chinese acupuncture in the treatment of ischemic stroke, and its effect on neurological function and activity of daily living

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Abstract

Purpose: *To investigate the clinical effect of combined use of Yiqi Huoxue Tongluo decoction and Chinese acupuncture on ischemic stroke, and its effect on neurological function and activity of daily living (ADL) of patients.*

Methods: *Three hundred and seventeen (317) ischemic stroke patients on admission at Ganzhou People's Hospital (GPH) were selected and randomly divided into acupuncture group (n = 159) and combination group (n = 158). Routine treatment of lesions was done for all patients. The acupuncture group was treated with Chinese acupuncture, while the combination group received a combination of Yiqi Huoxue Tongluo decoction and Chinese acupuncture. All treatments lasted for one month. Indicators such as clinical efficacy, neurological function and ADL were determined in each group.*

Results: *The combination group had significantly higher post-treatment objective response rate (ORR) than the acupuncture group ($p < 0.05$). The levels of growth differentiation factor-15 (GDF-15) and plasminogen activator inhibitor 1 (PAI-1) were significantly reduced in both groups, with significantly lower levels in the combination group than in acupuncture patients ($p < 0.05$). Varying degrees of decrease in neuropathy disability (NDS) scores were seen in both groups, and at 1 month and 3 months after treatment, the NDS scores of the combination group were lower than those of the acupuncture group ($p < 0.05$). Both groups had higher BI scores after treatment, but at 1 month and 3 months post-treatment, the BI scores of the combination group were significantly higher than those of the acupuncture group ($p < 0.05$).*

Conclusion: *The use of a combination of Yiqi Huoxue Tongluo decoction and Chinese acupuncture produced better clinical efficacy and lower serum levels of GDF-15 and PAI-1 than acupuncture, and it significantly improved the ADL of patients.*

Keywords: *Ischemic stroke, Neurological function, Chinese acupuncture, Yiqi Huoxue Tongluo decoction, Activity of daily living (ADL)*

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INTRODUCTION

Ischemic stroke refers to a cerebrovascular disease in which patients suffer from cerebral ischemia and hypoxia due to impaired blood supply to the brain, followed by brain tissue softening and necrosis, and formation of focal infarcts [1-4]. The clinical manifestations of ischemic stroke are sudden onset, adverse

events in limbs on one side, drooling of saliva, twisting of the eye and mouth to one side, and transient ischemic symptoms (i.e., dizziness and nausea, slurred speech, limb numbness, and transient black out before the onset) [5-8]. Other manifestations include hemiplegia, headache, tinnitus, and unconsciousness in severe cases which require emergency treatment [5-8]. Usually, if timely treatment is carried out, the patient's nerve defects are significantly alleviated within six months after onset, but the recovery of neurological function in patients with hypertension, diabetes and heart disease is poor [9-12]. In the clinic, western medical practitioners often use thrombolysis intervention, while TCM plays an important role in the rehabilitation phase. Acupuncture is a TCM treatment which has been repeatedly known to improve recovery from cerebral stroke by promoting blood circulation, thereby removing blood stasis and relieving rigidity of muscles. Moreover, acupuncture activates the tendons. Besides, TCM has unique advantages in enhancing the recovery of neurological function in cerebral stroke patients. However, there are limited studies on the use of combination of acupuncture and *Yiqi Huoxue Tongluo* decoction in the treatment of ischemic stroke patients in clinical medicine. Therefore, this study was aimed at investigating the efficacy of combined use of *Yiqi Huoxue Tongluo* decoction and acupuncture in the treatment of ischemic stroke patients, with respect to its effect on neurological function and activity of daily living (ADL).

METHODS

General patient information

A total of 317 ischemic stroke patients treated at GPH from January 2019 to December 2020 served as subjects in this study. They were selected and randomly divided into acupuncture group (n = 159) and combination group (n = 158). As shown in Table 1, the two groups were similar in terms of baseline data of patients.

Inclusion criteria

Patients who met the following criteria were included: patients who satisfied the criteria for clinical diagnosis of ischemic stroke as indicated in *China Guidelines for Cerebrovascular Disease Prevention and Treatment,* and were diagnosed with ischemic stroke after examinations such as cranial CT and MRI; patients who had blood stasis syndrome and *vital energy deficiency* syndrome as described in the *Diagnostic and Therapeutic Evaluation Criteria for Stroke Disease* (the general situation and TCM for diagnostic information on patients within 72 h after onset were obtained by the physician-in-charge, and if the quantitative diagnostic scores of the syndromes were not less than 7 points, a positive diagnosis was established); patients with no history of tongue muscle atrophy and swallowing disorders, and with intact pharyngeal reflex; and patients who survived during rescue and were successfully entering the rehabilitation phase to receive subsequent treatments.

Exclusion criteria

Patients with severe organ dysfunction and unstable vital signs, patients suffering from malignant tumors, patients for whom the treatments or examination used in this study were contraindicated, and those with poor compliance with the study.

This study was approved by the ethics committee of *Ganzhou People's Hospital* (approval no. = 20181140), and it was carried out in accordance with the Declaration of Helsinki as revised in 2013 [13]. The family members of the patients gave signed informed consent for the participation of the patients in this investigation.

Table 1: Clinical profile of patients

Variable	Acupuncture group (n=159)	Combination group (n=158)	t/λ^2	*P*-value
Age (years)	67.45±4.38	67.31±4.15	0.2921	0.7704
Duration of disease (h)	24.08±3.89	23.86±3.75	0.5126	0.6086
NIHSS score	17.05±5.12	17.14±5.23	0.1548	0.8771
Gender			0.0938	0.759
Male	99 (62.26%)	101 (63.92%)		
Female	60 (37.74%)	57 (36.08%)		
Complications			0.2718	0.602
Hypertension	69 (43.40%)	64 (40.51%)		
Hyperlipidemia	48 (30.19%)	48 (30.38%)		
Coronary heart disease	27 (16.98%)	30 (18.99%)		
Diabetes	15 (9.43%)	16 (10.13%)		

Treatments

All patients received routine treatment and rehabilitation training for one month, and were followed-up for three months.

Acupuncture group: *Baihui*, *Dazhui*, *Hegu*, *Fengchi*, *Quchi*, *Sanyinjiao* and *Zusanli* were selected as the major acupuncture points; while in the TCM differentiation, *Fenglong* and *Guanyuan* were selected as the matching acupoints for *phlegm-damp clouding* orifices; *Waiguan* and *Fenglong* were chosen for *wind-phlegm obstructing collateral*, and *Fenglong* and *Jianshi* were selected for excessive *fu-viscera* caused by *phlegm-heat*. *Fuliu* and *Taixi* were targeted at *stirring wind* due to *yin* deficiency; *Taixi* and *Taichong* were aimed at upward disturbance of hyperactive liver *yang*, while *Xuehai* and *Qihai* were targeted at blood stasis due to *qi* deficiency. *Dicang* and *Jiache* were added against twisting of the mouth; *Jiandu, Shousanli* and *Biru* were used against motor impairment of the upper limbs, while *Liangqiu, Huantiao* and *Xuanzhong* targeted motor impairment of the lower limbs.

A suitable position was selected according to the acupuncture points. Following routine disinfection with 75 % alcohol, 40 mm x 0.3 mm filiform needles were inserted into the *Fengchi* to depths of 0.8 - 1.2 cun, *Quchi* to depths of 0.8 - 1.2 cun, *Hegu* to depths of 0.5 - 1.0 cun, *Zusanli* to 1.0 - 1.2 cun, and *Sanyinjiao* to 1.0 - 1.5 cun. Acupuncture was performed once daily, with the needle manipulated twice for 30 min in each session. Patients in the combination group were orally given *Yiqi Huoxue Tongluo* decoction which was prepared from 30 g of mongolian milkvetch root, 20 g of danshen root, *Chinese angelica*, peach seed, peony root, safflower, Sichuan lovage rhizome, earthworm and leech (10 g each); 5 g of scorpion, and 1 - 3 centipedes, in addition to the treatment in the control group [14]. For liver yang and febrile disease complicated with wind pattern, 20 g of abalone shell, 15 g of gambir plant nod, 10 g of tall gastrodia tuber, and 10 g of two-toothed achyranthes root were added. Supplements of bile arisaema, snake gourd fruit and rhubarb root parched in wine (10 g each) were added for excessive fu-viscera caused by phlegm-heat and wind-phlegm. Patients with wind-phlegm, blood stasis and blockage of collaterals, needed the addition of 15 g of tuckahoe, 10 g of ginger-processed pinellia, 10 g of tabasheer, and 6 g of bile arisaema. The addition of 15 g of dwarf lilyturf tuber and 10 g of jujube peel was targeted at yin deficiency of liver and kidney. Abalone shell (15 g) and gambir plant nod (10 g) were added for eye distension and headache. Bad tendency of the upper limbs needed the addition of mulberry twig (15 g). Weakness of the lower limbs required the addition of two-toothed achyranthes root, Chinese viscum herb, eucommia bark and *Dipsacus asperoides* (10 g each). All herbs were decocted with warm water, and the patients took 1 dose per day in two split times (in the morning and evening) in two courses, each lasting for 15 days.

Evaluation of treatment indices

Clinical efficacy

The clinical efficacy of treatment in both groups of patients was evaluated using the criteria established in the 4th National Cerebrovascular Disease Conference Group [15]. The patients were considered as *cured* if clinical manifestations and adverse vital signs disappeared, with over 90 % decrease in nerve defect score, and disability level of 0. Treatment was *markedly effective* if clinical manifestations and adverse vital signs were significantly reduced, with 46 – 90 % decrease in nerve defect score, and disability level of 1-3. On the other hand, the treatment was *effective* if clinical manifestations and adverse vital signs were reduced, with 18 -45 % decrease in nerve defect score. However, the treatment was *ineffective* if the clinical symptoms were not reduced, and decrease in nerve defect score was less than 17 %. The objective response rate (ORR) was calculated as indicated in Eq. 1:

$$ORR\ (\%) = \{(C + ME + E)/N\}100 \quad \ldots\ldots\ldots\ldots (1)$$

where *C* = number of cured cases; *ME* = number of markedly effective cases, and *E* = number of effective cases, and N = total number of cases

Evaluation of levels of GDF-15 and PAI-1

Fasting elbow vein blood (3 mL) was collected from each of the patients in the morning. The blood samples for serum were put into plain tubes and allowed to stand for 1-2 h prior to centrifugation for 10 min at 3,000 rpm. The GDF-15 levels were measured in serum using ELISA method, with kits manufactured by Shanghai Xin Yu Biotech Co. Ltd. Serum PAI-1 was directly measured with ELISA method, using kits manufactured by Beijing Dingguo Changsheng Biotechnology Co. Ltd.

Neuropathy Disability Score (NDS)

Clinical Criteria of Neuropathy Disability Score for Acute Stroke Patients was used to score the

patients. The scale was based on 8 parameters, each of which was scored 0-6 points. The lower the scores, the lighter the degree of neuropathy disability.

Ability of daily living (ADL)

The post-treatment ADL of patients was evaluated with the Barthel Index (BI) which covered eating, dressing, adorning, bathing, defecation, stool control, urination control, walking on flat ground, moving beds or chairs, and going up or down the stairs. Each parameter was scored in the range, 0 - 10 points, and higher scores indicated better ADL.

Adverse reactions

Adverse reactions which occurred in patients in both groups during treatment were recorded.

Statistical analysis

The SPSS21.0 software was used for statistical analysis, while GraphPad Prism 7 was employed for graphics. Counted data were recorded as [n (%)], and were analyzed using λ^2 test. Measured data are expressed as mean ± SD, and analyzed with *t*-test. Values of $p < 0.05$ indicated significant differences.

RESULTS

Clinical efficacy

Table 2 shows that the ORR of the combination group was significantly higher than that of the acupuncture group ($p < 0.05$).

Levels of GDF-15 and PAI-1

After treatment, the GDF-15 and PAI-1 levels of patients in both groups were significantly lowered, but the levels in the combination group were significantly lower than those in the acupuncture group ($p < 0.05$; Table 3).

NDS scores

After treatment, different degrees of decrease were seen in the NDS scores of patients in both groups. At 1 month and 3 months after treatment, the NDS scores of the combination group were lower than those of the acupuncture group. These results are shown in Table 4.

ADL scores

Figure 1 shows that BI scores of patients were increased in both groups, but at 1 month and 3 months after treatment, the BI scores of the combination group were higher than those of the acupuncture group.

Incidence of adverse reactions

There were no statistically significant differences in total incidence of adverse reactions between the two groups ($p > 0.05$; Table 5).

DISCUSSION

The number of cases of ischemic stroke is on the increase due to factors such as increased socioeconomic status, changes in people's lifestyles, and enhanced longevity.

Table 2: Clinical efficacy [n (%)]

Variable	Acupuncture group (n=159)	Combination group (n=158)	λ^2	*P*
Ineffective	19 (11.95)	8 (5.06)		
Effective	48 (30.19)	44 (27.85)		
Markedly effective	47 (29.56)	52 (32.91)		
Cured	45 (28.30)	54 (34.18)		
ORR	140 (88.05)	150 (94.94)	4.823	0.03

Table 3: GDF-15 and PAI-1 levels (mean ± SD)

Group		Acupuncture (n=159)	Combination (n=158)	*t*	*P*
GDF-15 (pg/ml)	Before	792.85±59.46	794.13±60.09		
	After	656.21±51.24	587.91±50.43	11.96	0.000
PAI-1 (mg/L)	Before	51.25±9.06	50.67±9.54		
	After	45.93±6.65	41.39±7.52	5.69	0.000

Table 4: Comparison of NDS scores between the 2 groups (mean ± SD)

Group	n	Before treatment	1 month after treatment	3 months after treatment
Acupuncture	159	27.05±7.14	22.65±5.73	20.51±4.16
Combination	158	26.98±6.95	19.02±4.61	15.73±3.05
t			6.2120	11.6607
P			< 0.001	< 0.001

Table 5: Incidence of adverse reactions [n (%)]

Group	Subcutaneous hemorrhage	Nausea and vomiting	Total incidence of adverse reactions
Acupuncture (n=159)	3 (1.89)	4 (2.52)	7 (4.40)
Combination (n=158)	3 (1.90)	5 (3.16)	8 (5.06)
λ^2			0.0768
P			0.782

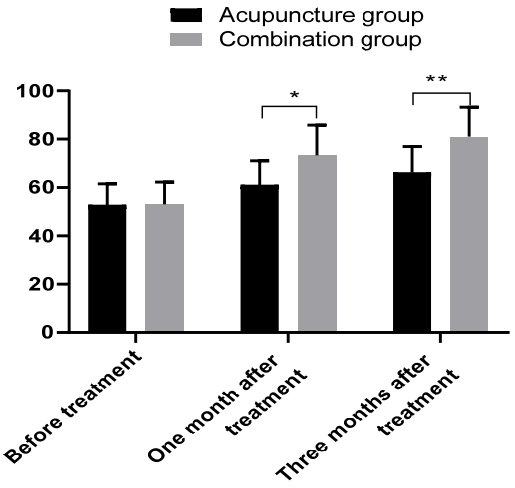

Figure 1: ADL scores of the two groups. *p < 0.001, BI score in acupuncture group vs BI score in combination group at 1 month after treatment; **p < 0.001, BI score in acupuncture group vs BI score in combination group at 3 months after treatment

Clinical treatment and prognostic rehabilitation are very important for ischemic stroke patients. In TCM, it is believed that ischemic stroke is mostly caused by internal factors such as endogenous *wind-evil* due to *mental anger* and a rise in *heart fire*; *hepatic wind* due to irregular diet, *phlegmatic stagnation* induced *heat-transmission*, and dysfunctional *spleen in transportation*; or disturbance of *wind generation* by *yang deficiency* due to *excessive fatigue* and *loss of yin* and blood internally. All these are syndromes of brain *qi* and *blood stagnancy* and *blocked collateral* which should be treated by "relieving rigidity of muscle, activating collateral and promoting blood circulation to remove blood stasis". It has been reported that *Yiqi Huoxue Tongluo* decoction regulated *qi* and blood, relieved muscle rigidity, and *activated the collaterals*, thereby effectively alleviating acute stroke symptoms, and mitigating nerve defects, all of which led to enhanced clinical efficacy [16].

This study has demonstrated that after treatment, the ORR of the combination group was markedly higher than that of the acupuncture group. The NDS scores of patients were increased in both groups, and at 1 month and 3 months after treatment, the combination group had significantly lower NDS scores than the acupuncture group. These results are consistent with the aforesaid finding [16]. After treatment, the levels of GDF-15 and PAI-1 in both groups were significantly reduced, with significantly lower levels in the combination group than in the acupuncture group.

In a study, it was found that growth differentiation factor 15 (GDF-15) was a new marker of neurologic impairment which was positively associated with defects in neurological function, while plasminogen activator inhibitor 1 (PAI-1) was positively associated with the disease severity [17]. Thus, PAI-1 and GDF-15 may serve as indexes in evaluating the conditions of ischemic stroke patients. This is consistent with the results of the present study. The post-treatment BI scores of patients in both groups were increased, and at 1 month and three months after treatment, the BI scores were significantly higher in combination group than in acupuncture group. There were statistically significant differences in incidence of adverse reactions between the two groups, implying that both treatments did not cause obvious adverse outcome to the patients. However, the clinical value of the combined treatment was better than that of acupuncture.

Yiqi Huoxue Tongluo decoction contained mongolian milkvetch root, Chinese angelica, peony root, peach seed, safflower, earthworm, leech, Sichuan lovage rhizome, danshen root,

scorpion and centipede. In TCM, the decoction is used for activating *meridians* and *collaterals*, invigorating *qi* and activating blood. Mongolian milkvetch root is the basic remedy that benefits *qi* for promotion of production of blood, and invigorating *qi* for increase in *yang*. Chinese angelica, peony root, peach seed, safflower, Sichuan lovage rhizome and danshen root promote blood circulation, thereby effectively inhibiting the surface activity of platelets. Moreover, they alleviate thrombosis by preventing blood agglutination. Leech, scorpion and centipede produce relief from spasms, eliminate blood stasis, *dredge the meridians*, and drain chronic blood stasis. According to *Yixue Zhongzhong Canxilu* [18], the centipede has the fastest speed for internal migration to the organs and external migration to the meridians. Thus, it acts on the brain and regulates brain nerves. In addition, acupuncturing *Baihui* invigorates splenic yang and enhances visceroptosis, consciousness-restoring resuscitation, and tranquilization. These attributes make it suitable for treating diseases such as hypertension, vascular headache and dizziness. Acupuncturing *Dazhui* invigorates *qi* for strengthening *yang*, which makes it useful for treating syndromes such as deficiency of five kinds of strain, seven types of injury-induced fatigue and neck rigidity. Acupuncturing *Hegu* activates the *meridians* and *collaterals,* and it exerts sedative and analgesic effects. Thus, it works well in the treatment of headache, eye and mouth twists, and other diseases. Acupuncturing *Quchi* relieves superficies syndrome by expelling wind and warm *yang* for dispelling cold. Thus, it is suitable for shoulder pain, numbness at the upper extremities, and hypertension. Acupuncturing *Zusanli* tonifies the spleen for nourishing *qi,* and supports healthy energy needed for eliminating pathogenic factors. These features make it useful for treating diseases such as hypertension and hyperlipidemia. Acupuncturing *Sanyinjiao* regulates liver and tonifies the kidney, and it invigorates the spleen and blood. Therefore, it is mainly used for *yin* deficiency, rheumatic arthritis and hypertension. Needling relevant acupoints could effectively improve cerebral blood circulation, establish *collateral circulation*, stimulate motor cortex excitation, and alleviate limb muscle tension while mitigating functional disorder at the same time.

Limitations of the study

This study was focused on analysis of the short-term treatment efficacy in patients, without long-term follow-up. Therefore, there is a lack of analysis on the long-term effect of treatment with combination of *Yiqi Huoxue Tongluo* decoction and Chinese acupuncture on ischemic stroke. In subsequent studies, attention will be paid to the long-term efficacy of the combination treatment.

CONCLUSION

Compared with treatment with TCM acupuncture alone, the use of a combination of *Yiqi Huoxue Tongluo* decoction and TCM acupuncture results in better clinical efficacy and lower serum levels of GDF-15 and PAI-1, ands positively impacts the recovery of neurological function and daily living ability of ischemic stroke patients. Thus, the combined treatment needs to be tested clinical trial.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. ZH and XZ conceived and designed the study, and drafted the manuscript. ZH, FL, BX and XZ collected, analyzed and interpreted the experimental data. ZH and FL revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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