Original Article
Treatment of late-onset epilepsy after cerebral hemorrhage by integrated traditional Chinese medicine and western medicine

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Abstract: Background: Epilepsy is the second commonly-occurred neurological disorder after stroke, and the cerebrovascular disease is the most common cause of secondary epilepsy. Purpose: To investigate the clinical efficacy of integrated traditional Chinese medicine and western medicine (TCM-WM) in treatment of late-onset epilepsy after cerebral hemorrhage. Methods: 60 patients with late-onset epilepsy after cerebral hemorrhage were divided into control group and TCM-WM group, which were treated with loading dose of sodium valproate and 1/2 loading dose of sodium valproate combined with 18 g of Chinese traditional medicine (TCM) (developed from the *Lingjiao Gouteng* decoction). The efficacy of TCM syndrome, epilepsy seizure frequency, electroencephalogram (EEG), life quality, cognitive function and safety of each group were observed at the middle of and after treatment. Results: After treatment, the epilepsy seizure times in TCM-WM group were significantly less than control group (P < 0.05). The total effective rate of TCM syndrome in TCM-WM group was 82.8%, which was significantly higher than 71.4 % in control group (P < 0.05). The total effective rates of EEG in TCM-WM group and control group were 82.7% and 57.1%, respectively, with significant difference between them (P < 0.05). The life quality score in TCM-WM group was 24.91±11.48, significantly lower than 29.46±14.59 in control group (P < 0.05), and the full-scale intelligence quotient in TCM-WM group was 84.73±10.74, significantly than 69.26±11.49 in control group (P < 0.05). There was no obvious adverse reaction after treatment in each group. Conclusion: The TCM-WM integrated treatment has good efficacy and safety for patients with late-onset epilepsy after cerebral hemorrhage.

Keywords: Epilepsy, treatment, traditional Chinese medicine, efficacy, safety

Introduction

Epilepsy is the second commonly-occurred neurological disorder after stroke, and the cerebrovascular disease is the most common cause of secondary epilepsy [1]. It is found that, the incidence of post-stroke epilepsy in people more than 60 years old accounts for about 45% of epileptic seizure [2]. The long-term application of anti-epileptic drugs will make the efficacy reduced, which is the result of body adaptive response and drug resistance. After the drug resistance appears, the side effects reduce, while the efficacy will also be lost [3]. At the same time, with the applications of anti-epileptic drugs, the drug-induced epileptic seizure has gradually obtained widespread concerns [4]. The treatment towards late-onset epilepsy

after cerebral hemorrhage has already become an intractable problem. This study was designed to apply integrated traditional Chinese medicine and Western medicine (TCM-WM) (*Lingjiao Gouteng* decoction combined with sodium valproate) to treatment of late-onset epilepsy after cerebral hemorrhage, and the clinical efficacy was investigated. The objective was to improve the therapeutic efficacy of late-onset epilepsy after cerebral hemorrhage, and reduce the amount of sodium valproate and its toxic side effects.

Subjects and methods

General data

60 patients with late-onset epilepsy after cerebral hemorrhage in the Affiliated Yantai

Table 1. Baseline characteristics of patients

Index*	TCM-WM group (30)	Control group (30)	x^2/t	P
Gender (male/female)	16/14	15/15	0.07	0.65
Age (year 3)	64.85±11.26	66.22±12.33	1.31	0.24
Weight (kg)	62.03±12.36	58.71±10.85	1.29	0.17
Duration of cerebral hemorrhage (years)	5.21±3.2	5.12±3.02	0.09	0.93
Duration of epileptic seizure (years)	5.32±3	6.35±4.28	0.90	0.37
SBP (mmHg)	135.65±44.51	131.72±50.30	0.09	0.88
DBP (mmHg)	76.89±11.58	71.16±10.51	0.46	0.51
Accompanied with coronary heart disease (n)	19	21	1.3	0.24
Accompanied with hypertension (n)	25	26	0.20	0.58
Accompanied with diabetics (n)	18	17	0.57	0.39
Family history of cerebrovascular disease (n)	16	20	1.25	0.23
TG (mmol/L)	2.9±0.8	3.0±0.7	0.58	0.50
HDL (mmol/L)	1.34±0.78	1.31±0.69	0.27	0.71
LDL (mmol/L)	5.260±1.32	5.79±1.96	1.32	0.39

*There was no significant difference of each index between 2 groups (P > 0.05). SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Traditional Chinese Medicine Hospital, Shandong University of Traditional Chinese Medicine (Yantai, China) from 2005 to 2010 were enrolled in this study. The inclusion criteria were as follows: (i) met the clinical criteria of epilepsy published by the International Union of anti-epilepsy in 2001 [5] and syndrome differentiation and classification criteria of traditional Chinese medicine (TCM) (Guiding Principle of Clinical Research on New TCM, 1995); (ii) met the diagnostic criteria of late-onset epilepsy after cerebral hemorrhage; (iii) aged 40-80 years. The exclusion criteria were as follows: (i) non-epileptic seizure; (ii) progressive, malignant or deformative disease; (iii) during the pregnant and lactating period; (iv) accompanied with kidney stones; (v) the patient could not keep the medication in time and fill the observation diary.

All patients were randomly divided into control group and TCM-WM group, 30 cases in each group, which would be treated with western medicine and TCM, respectively. The baseline characteristics of patients were shown in **Table 1**. There was no significant difference of each index between 2 groups (P > 0.05). During this study, 2 and 1 cases fell off from the control group and TCM-WM group, respectively. Finally 28 and 29 cases in control group and TCM-WM group completed the follow-up, respectively. This study was approved by the ethics committee of Affiliated Yantai Traditional Chinese Medicine Hospital, Shandong University of Traditional Chinese Medicine. A written informed consent was obtained from all participants.

Treatment methods

According to the double-blind test requirement, the control group and TCM-WM group were administrated with loading dose of sodium valproate and 1/2 loading dose of sodium valproate combined with 18 g of TCM, twice a day. The TCM was developed from the *Lingjiao Gouteng* decoction, which composed of antelope antelope horn, *uncaria rhynchophylla*, *florists dendranthema*, *radix paeoniae alba* and stiff silkworm. The quality was controlled according to Pharmacopoeia of the Peoples Republic of China. It was prepared and packaged (9 g in each bag) in Affiliated Yantai Traditional Chinese Medicine Hospital, Shandong University of Traditional Chinese Medicine, and stored at 4°C for use. The 2 groups were treated for 104 weeks, and the indicators of efficacy and safety were observed at the middle of and after treatment. The appearance, size and color of medication in 2 groups were consistent, and the blind test was performed for 3 times. If the severe adverse event appeared, it should be reported and the blind should be uncovered. The efficacy evaluation and statistical analysis were also performed using blind methods.

Table 2. Therapeutic effect in 2 groups

Group	Clinically cured (n)	Significantly effective (n)	Effective (n)	Invalid (n)	Total effective rate (%)#
Control (28)	12	4	4	8	71.4
Treatment (29)	17	3	4	5	82.8*

#Total effective rate: clinically cured + significantly effective + effective; *P < 0.05 compared with control group.

Observation indicators

The efficacy indicators were as follows: (1) TCM syndrome efficacy. According to the Guiding Principles for Clinical Research of Treatment of Epilepsy Using New TCM (Ministry of Health of China, 1993), the TCM syndrome efficacies were classified as follows: (i) Clinically cured: the seizure was fully controlled for 2 years, and EEG returned to normal. (ii) Significantly effective: the seizure frequency was reduced by more than 75%, or without onset for more than 6 months. The EEG change was significantly improved. (iii) Effective: the seizure frequency was reduced by 50-75%, or the symptoms of onset were significantly reduced. The duration was shortened by more than 1/2, and the EEG change was improved. (iv) Invalid: the seizure frequency, extent, symptoms of disease onset and EEG had no obvious improvement or became worse. In these criteria, the seizure frequency, duration and EEG change were combined to comprehensively evaluate the efficacy. (2) Seizure frequency. (3) EEG performance: the scalp EEG diagnostic classification scheme was established according to previous methods [6]. (4) Quality of life. The quality of life was evaluated using Minnesota life quality scale. (5) Cognitive function. The cognitive function of patient was tested according to Wechsler Adult Intelligence Scale revised (Chinese Revised edition, 1982), using full-scale intelligence quotient (FIQ) as index. The total scale > 81 points, 71-80 points, 61-70 points, and < 60 points were considered as normal, mild cognitive impairment, moderate cognitive impairment, and severe cognitive impairment, respectively. (6) Safety indicators. The adverse events and abnormality were confirmed by laboratory test in the blood routine, urine routine, stool routine, liver function, renal function, etc.

Follow-up

The follow-up was conducted, involving the medication, clinical symptoms and other concomitant therapies.

Statistical analysis

Data were expressed as mean ± SD. Statistical analysis was performed using SPSS 17.0 statistical software. A t-test was used to analyze the differences between two groups. The rank sum test was performed for non-normal distribution or heterogeneity of variance. The counting data were expressed as composition ratio and rate, and the intergroup comparison was conducted using chi-square test. P < 0.05 and P < 0.01 were considered as statistically significant and highly statistically, respectively.

Results

Comparison of therapeutic effect between 2 groups

As shown in **Table 2**, the total effective rates of TCM syndrome in control group and TCM-WM group were 82.8% and 71.4%, respectively, with significant difference between them (P < 0.05).

Comparison of epilepsy seizure frequency after treatment between 2 groups

The 6-month epilepsy seizure frequencies after treatment in 2 groups were compared. There were 8.8±3.5 times of 6-month epilepsy seizure after treatment in TCM-WM group, which were significantly less than 11.9±4.7 times in control group (P < 0.05).

Comparison of EEG changes between 2 groups

Before treatment, in 60 patients, 52 cases exhibited spontaneous or induced complex of spike and slow waves, or paroxysmal high-amplitude slow waves. In 6 cases, the electrical activity of brain became slow, or the bilateral amplitudes were asymmetry, with non-synchronic rhythm. 2 cases (1 case in each group) had normal EEG. After treatment, 57 patients reviewed EEG reexamination. In 18 cases, the paroxysmal spike and slow waves of decreased or disappeared, and replaced by the paroxysmal slow waves or scattered slow waves. In 25 cases, the epileptic discharge completely disappeared, and the electrical activity of brain was restored to normal. There were 16 and 24 cases of improvement (normal + improved) in

Table 3. EEG changes in 2 groups

Group	Normal (n)	Improved (n)	No change (n)	Aggravated (n)	Total effective rate (%)#
Control (28)	9	7	8	4	57.1
Treatment (29)	14	10	4	1	82.7*

#Total effective rate: normal + improved; *P < 0.05 compared with control group.

Table 4. Minnesota life quality scores in 2 groups (mean ± SD)

Group	Time	Cases (n)	Life quality score (point)
Control	Before treatment	30	40.56±17.38
	After treatment	29	29.46±14.59*
Treatment	Before treatment	30	37.41±15.75
	After treatment	28	24.91±11.48*,#

*P < 0.01 compared with before treatment; #P < 0.05 compared with control group after treatment.

Table 5. Cognitive function in 2 groups (mean ± SD)

Group	Time	Cases (n)	FIQ
Control	Before treatment	30	79.19±9.49
	After treatment	29	69.26±11.49*
Treatment	Before treatment	30	77.59±10.67
	After treatment	28	84.73±10.74*,#

*P < 0.01 compared with before treatment; #P < 0.05 compared with control group after treatment. FIQ, full-scale intelligence quotient.

control group and TCM-WM group, respectively, and the total effective rates were 57.1% and 82.7%, respectively, with significant difference between them (P < 0.05) (**Table 3**).

Comparison of quality of life between 2 groups

The Minnesota life quality scores in 2 groups were shown in **Table 4**. Before treatment, there was no significant difference life quality score between 2 groups (P > 0.05). After treatment, the life quality score in each group was significantly lower than before (P < 0.01), and that in TCM-WM group was significantly lower than control group (P < 0.05).

Comparison of cognitive function between 2 groups

As shown in **Table 5**, the cognitive functions in TCM-WM group and control group had no significant difference before the treatment (P > 0.05). After treatment, FIQ in control group was significantly lower than before (P < 0.01), while that in TCM-WM group was significantly higher than before (P < 0.01). There was significant difference between 2 groups (P < 0.05).

Comparison of treatment safety between 2 groups

After treatment, there was no obvious abnormality of blood routine, urine routine, stool routine, liver function or renal function in each 2 group.

Discussion

Epilepsy after cerebrovascular disease is divided into the early-onset type and late-onset type [7]. The incidence of epilepsy is related with the balance disorders of excitatory and inhibitory neurotransmitter [8]. Glutamic acid and γ-aminobutyric acid (GABA) play an important role in maintaining the balance of excitation and inhibition, as well as in the pathogenesis of epilepsy [9-12]. The early-onset type epilepsy after cerebral hemorrhage is the outcome of abnormal electrical activities induced by cellular biochemical dysfunction. The acute hemorrhage causes the increased concentration of extracellular glutamate, which acts as the excitatory neurotransmitter associated with the secondary nerve injurie [13]. GABA is the major inhibitory central neurotransmitter. GABA and its receptor widely exist in the brain tissues such as hippocampus, amygdala and cerebral cortex, playing an important role towards the occurrence of epilepsy and other diseases [14-16]. The production and release abnormalities of GABA are the important cause of epilepsy [17]. The late-onset type epilepsy is due to the glial cell proliferation and occurrence and development of meninges scars [18]. The change in cell membrane, selective neurological deficit and formation of collateral branch can cause the excessive excitability and synchronic neuronal discharging, thus resulting in the epileptic seizure [19, 20].

In TCM the epilepsy refers to that, the organs are injured, thus involving in the vital activities in vivo. The primordial spirit experiences the

loss of control. The patient exhibits the major clinical such as suddenly and unconsciously falling down to the ground, with two eyes becoming white visible, vomiting salivation, twitching the limbs or strangely shrieking at the same time. When the patient is shifted, he will wake, exhibiting normal manifestations. In the *Suwen Pain theory*, there are expressions of terror collapsing *Qi* and scare disorder *Qi*. Due to the sudden shocking, the patient exhibits huge fear, causing turbulent *qi* and spirit, and thus damaging the internal organs. When the liver and kidney are damaged, the *Yin* can not gather the *Yang*, thus generating the heat and restlessness. Then the spleen and stomach will be damaged and the subtle and minor substances can not distribute evenly. The phlegm and turbid gather inside, and will not disappear for a long time. Once the patient receives the stimulus, the phlegm or turbid will move reversely against the *Qi*, or together with the wind, causing the brain to be blocked and closed, so the epilepsy is generated.

According to the symptoms of epilepsy, the TCM treatment is mainly concentrated on calming the liver and stopping the wind, eliminating the phlegm blockage and opening the resuscitation. However, there is less report on TCM treatment for. This study is focused on the characteristics of late-onset epilepsy after cerebral hemorrhage. Cooling the liver and stopping the wind in TCM theory are used as the starting points, with simultaneous treatment of principal and subordinate symptoms. It is carried out on the basis of our long-term clinical observation and adequate investigation. The objective is to control or slow the progression of late-onset epilepsy after cerebral hemorrhage, greatly improve the clinical efficacy, relieve the physical and mental pain of patients, and substantially improve or restore their live and labor ability.

The components and functions of *Lingjiao Gouteng* decoction are as follows: antelope horn, *uncaria rhynchophylla*, cooling the liver, stopping the wind and releasing the heat and spasm; *florists dendranthema* and *concha haliotidis*: strengthening the effect of cooling wind; *radix paeoniae alba* and *rehmannia dride rhizome*: softening the liver and tendons; *bulbus fritillariae cirrhosae* and *caulis bambusae in taenam*: clearing the heat and dissipating the phlegm; *radix acanthopanacis bidentatae*: leading the blood downward, thus cooling down the blood inversion; *bombyx batryticatus*: ceasing the wind and stopping the spasm; *Concretio Silicea Bambusae*: cooling the heat and eliminating the phlegm; *acorus calamus*: eliminating the phlegm and opening the resuscitation; *glycyrrhiza uralensis*: reconciling the various drugs. This study is designed to combine lingjiao Gouteng decoction with sodium valproate, and observe the clinical efficacy of TCM-WM towards late-onset epilepsy after cerebral hemorrhage, in order to improve the treatment efficacy, while appropriately reduce the amount of sodium valproate and its toxic side effects. Based on this, the randomized double-blind controlled trial with more rigorous clinical design study is performed in this study. Results confirm that, on the basis of western medicine treatment, the TCM-WM group exhibits greater amelioration of clinical symptom than control group, with improved cognitive function and quality of life. In TCM-WM group, the epilepsy seizure times were significantly less than control group. The clinical improvement of epilepsy patients are basically the same with EEG changes, which also confirmed the effects of TCM from the physiological point of view. TCM has good effect to reduce the epilepsy seizure after cerebral hemorrhage. However, the mechanism was still unclear, and needs to be further investigated.

In terms of safety, there is no significant adverse reaction in both 2 groups, indicating that TCM is safe and reliable. Currently the expensive medical expense using western medicine in treatment of epilepsy after cerebral hemorrhage has affected the compliance of patients to some extent. Furthermore, due to a variety of adverse reactions, some patients have difficulty to accept the best treatment solution. In treatment of late-onset epilepsy after cerebral hemorrhage, TCM has the characteristic of improved efficacy, less cost and reduced adverse reactions. It has a bright application future.

Disclosure of conflict of interest

None.

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