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Effect of Geteng Tongluo Capsule Combined with Fluoxetine on Inflammatory Factors and Neurotransmitters in Patients with Post-stroke Dementia

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Keywords

Geteng Tongluo capsule, Fluoxetine, Post-stroke dementia, Inflammatory factors, Neurotransmitters

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Abstract

Objective To explore the effect of Getong Tongluo capsules combined with fluoxetine on inflammatory factors and neurotransmitters in patients with post-stroke depression (PSD). **Methods** 112 patients with PSD who were treated in our hospital from January 2019 to October 2021 were randomly divided into a control group and an observation group, with 56 cases in each group. Patients in both groups were given conventional treatment with Western medicine, based on which fluoxetine was given to the control group, while the observation group was treated with Getong Tongluo capsules on the basis of the control group. Clinical efficacy, inflammatory factor levels, neurotransmitter levels, and national institutes of health stroke scale (NIHSS) and Hamilton depression scale (HAMD) scores were compared between the two groups. **Results** The total effective rate of the observation group was markedly higher than that of the control group (P<0.05). After treatment, the levels of interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), S100-β protein and NIHSS and HAMD scores were significantly lower than those before treatment (P<0.05), and those of the observation group were significantly lower than those of the control group (P<0.05). After treatment, the levels of nerve growth factor (NGF) and dopamine (DA) in the two groups were significantly higher than those before treatment (P<0.05), and those of the observation group were significantly higher than those of the control group (P<0.05). **Conclusion** The combination of Getong Tongluo capsules combined with fluoxetine can effectively alleviate the clinical symptoms of PSD patients, reduce the inflammatory response, regulates neurotransmitters NGF, DA, and S100-β levels, and alleviate the depression of patients.

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Introduction

Stroke is a common cerebrovascular disease in the clinic, and there are serious sequelae such as limb disability, paralysis, and cognitive dysfunction. As the patient's neurological deficit, stroke greatly reduces the patient's quality of life and economic level, which in turn induces bad emotions such as anxiety and depression, and secondary post-stroke depression (PSD). A previous study have shown that the incidence of depression in patients with stroke is as high as 33.5% within 7 years [1]. At present, the main methods for clinical treatment of PSD include antidepressants, psychological interventions, and traditional Chinese medicine treatment. Fluoxetine is a widely used 5-hydroxytryptamine (5-HT) reuptake inhibitor with antidepressant effects, but the continuous usage of fluoxetine is prone to gastrointestinal dysfunction, sleep abnormalities and many other adverse reactions, which will lead to a limitation of clinical use [2]. In recent years, traditional Chinese medicine has gradually been accepted by PSD patients and doctors who treat PSD due to its advantages of few side reactions and good long-term efficacy. Besides, Chinese medicine doctors believe that PSD belongs to the categories of "apoplexy" and "depression", which is caused by sputum clouding and liver qi depression, and Geteng Tongluo capsule is a Chinese medicine compound capsule preparation for the treatment of ischemic stroke, which has the effects of activating meridians as well as blood, and promoting the circulation of qi [3]. At present, there are few studies of Geteng Tongluo capsule combined with fluoxetine in the treatment of patients with PSD, and this study aims to explore the impact of Geteng Tongluo capsule combined with fluoxetine on the clinical symptoms, inflammatory factors and the neurotransmitters levels of patients with PSD so as to provide a reference for clinical treatment, and the results of the study are reported as follows.

Data and methods

General information

112 patients with PSD treated in our hospital from January 2019 to October 2021 were selected as the research subjects, and randomly divided into observation group (n=56) and control group (n=56). There was no significant difference in gender, age, body mass index, disease type and depression course between the two groups (P>0.05), as shown in Table 1. This study was approved by the medical ethics committee, and all patients were informed and agreed.

Table 1. Comparison of general data between the two groups

Group		The observation group（n=56）	The control group（n=56）	χ2/t	P
Gender（case）	Male	29	31	0.144	0.705
	Female	27	25		
Age (year)		58.62±9.34	58.89±8.80	-0.157	0.875
Body mass index（kg/m2）		22.55±2.37	23.29±2.05	-1.767	0.080
Course of depression （d）		27.15±4.12	27.31±4.26	-0.202	0.840
Type of disease（case）	Cerebral Hemorrhage	22	20	0.152	0.696
	Cerebral infarction	34	36		

Inclusion criteria

(1) Those patients who met the diagnostic criteria of Chinese guidelines for diagnosis *and treatment of acute ischemic stroke 2018* [4] of Chinese Society of Neurology, and were diagnosed as stroke by computerized tomography (CT), magnetic resonance imaging (MRI) and other imaging examinations. (2) Those patients whose score ≥2 based on *Correlation*

between sympathetic skin response and plasma dopamine, serotonin and HAMD scores in patients with post-stroke depression [5]. (3) The patients' clinical data were complete and the compliance of patients was good, and there was no history of drug allergy.

Exclusion criteria

(1) Patients with pre-stroke depression. (2) Patients with severe language function, physical function, cognitive dysfunction, epilepsy, bipolar disorder and other serious mental diseases. (3) Patients with heart, liver, kidney and other organ dysfunction. (4) Patients who recently took sertraline, citalopram and other antidepressants.

Treatment Methods

Patients in both groups were given routine western medicine treatment for stroke, such as neuroprotection, blood pressure control and anti-platelet aggregation. The control group was given fluoxetine hydrochloride tablets (Changzhou Siyao Pharmaceutical Co., Ltd., approval number of National Medical Products Administration:.H19980139, specification: 10mg*14 tablets) once a day, whlie the observation group was given Geteng Tongluo capsule (Anhui Jiufang Pharmaceutical Co., Ltd., approval number of National Medical Products Administration: Z20060439, specification: 0.25g*12 tablets*2 plates), and took two tablets once and two times a day on the basis of the control group. In addition, both groups were treated for 8 weeks.

Test indicators

(1) HAMD and national institutes of health stroke scale (NIHSS) [6] score: before and after 8 weeks of treatment, HAMD was used to evaluate the depression status of the two groups patients, and the scoring criteria were as follows: normal: <7 points; have the possibility of depression: ≤17 points; definite depression: ≤24 points; severe depression: >24 points. The higher the HAMD score calculated, the higher the degree of depression presented. At the same time, NIHSS was used to evaluate the neurological function of the two groups patients, and the scoring criteria were as follows: normal: ≤1 point; mild stroke: ≤4 points; moderate stroke: ≤15 points; moderate and severe stroke: ≤20 points; severe stroke: >20 points. The higher calculated NIHSS score indicated, more severity of the nerve damage. (2) Clinical efficacy [7]: the clinical efficacy was evaluated according to the HAMD of the two groups patients before and after 8 weeks of treatment. The evaluation criteria were: recovery: HAMD score decreased by ≥ 75%; obvious effect: HAMD score decreased by ≥ 50%; effective: HAMD score decreased by ≥ 25%; ineffective: HAMD score decreased < 25% or increased, and the total effective rate=(cured cases+ obvious effect cases+effective cases)/total cases× 100%; (3) Inflammatory factor as well as neurotransmitter level: 5mL fasting venous blood of patients in two groups was taken for inspection in the morning before and after 8 weeks of treatment. Moreover, Interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), S100-β protein and nerve growth factor (NGF) were detected by ELISA.

Statistical methods

SPSS 20.0 was used for statistical analysis, the counting data were compared by χ^2 test, the measurement data were expressed by mean ± standard deviation ($\bar{x}\pm s$), and the comparison between the two groups was made by independent sample *t* test, and the comparison between different time points in the same group was made by paired sample *t* test. Besides, the data were statistically significant when $P<0.05$.

Results

Comparison of clinical efficacy of patients between two groups

The total effective rate in observation group was significantly higher than that in control group ($P<0.05$), which were enumerated in Table 2.

Table 2. Comparison of clinical efficacy of patients between two groups [cases (%)]

Group	Case	Recovery	Obvious effect	Effective	Ineffective	The total effective rate
The observation group	56	14（25.00）	20（35.71）	15（26.79）	7（12.50）	49（87.50）
The control group	56	10（17.86）	16（28.57）	14（25.00）	16（28.57）	40（71.43）
χ^2						4.432
P						0.035

Comparison of inflammatory factors of patients between the two groups

Before treatment, there was no significant difference in IL-1β, TNF-α and CRP levels between the two groups (P>0.05). After treatment, the levels of IL-1β, TNF-α and CRP in the two groups were significantly decreased (P<0.05), and the levels of IL-1β, TNF-α and CRP in observation group were significantly lower than those in control group (P<0.05), as described in Table 3.

Table 3. Comparison of inflammatory factors between two groups ($\bar{x}\pm s$)

Group	Case	IL-1β（μg/L）		TNF-α（μg/L）		CRP（mg/L）	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
The observation group	56	37.75±3.84	21.37±4.03*	27.73±4.47	12.10±2.36*	10.31±1.22	3.97±0.50*
The control group	56	37.09±4.03	28.14±3.31*	28.48±4.02	20.12±2.55*	10.14±1.32	6.97±0.85*
t		0.887	-9.715	-0.934	-17.273	0.708	-22.765
P		0.377	0.000	0.353	0.000	0.481	0.000

Note: Compared with pre-treatment data *P<0.05

Comparison of neurotransmitter levels of patients between the two groups

Before treatment, there was no significant difference in NGF, DA and S100-β levels between the two groups (P>0.05). After treatment, NGF and DA levels in the two groups were significantly enhanced (P<0.05), and NGF and DA levels in observation group were obviously higher than those in control group (P<0.05). After treatment, the level of S100-β in the two groups was significantly reduced (P<0.05), and the level of S100-β in observation group was significantly lower than that in control group (P<0.05), as listed in Table 4.

Table 4. Comparison of neurotransmitter levels of patients between the two groups （$\bar{x}\pm s$）

Group	Case	NGF（mg/mL）		DA（ng/mL）		S100-β（ng/L）	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
The observation group	56	6.13±1.11	12.06±1.29*	32.63±5.22	67.72±7.01*	1.84±0.19	0.69±0.07*

The control group	56	6.30±0.91	9.04±1.36*	33.00±5.46	52.51±5.14*	1.78±0.26	1.32±0.18*
t		-0.886	12.056	-0.367	13.094	1.394	-24.411
P		0.378	0.000	0.715	0.000	0.166	0.000

Note: Compared with pre-treatment data: *P<0.05

Comparison of NIHSS and HAMD scores between the two groups

Before treatment, there was no significant difference in NIHSS and HAMD scores between the two groups (P<0.05). After treatment, the NIHSS and HAMD scores in the two groups were significantly reduced (P<0.05), and the NIHSS and HAMD scores in observation group were significantly lower than those in control group (P<0.05), as shown in Table 5.

Table 5. Comparison of NIHSS and HAMD scores between the two groups （$\bar{x}$±s）

Group	Case	NIHSS score		HAMD score	
		Before treatment	After treatment	Before treatment	After treatment
The observation group	56	25.08±2.62	11.94±1.09*	22.00±2.16	8.82±0.75*
the control group	56	24.92±2.74	19.18±1.62*	21.78±2.18	13.40±1.42*
t		0.316	-27.748	0.536	-21.342
P		0.753	0.000	0.593	0.000

Note: Compared with pre-treatment data: *P<0.05

Discussion

PSD patients are mainly characterized by depression, lack of interest, energy decline, reluctance to communicate with medical staff, decreased compliance with medical orders. Even suicidal tendencies would occur in severe cases. Moreover, PSD not only increases the disability rate and death rate of stroke, but also increases the recurrence rate of stroke, seriously affecting the prognosis of patients, so the diagnosis and treatment of PSD is particularly important [5,8]. Western medicine such as sertraline, fluoxetine and other antidepressants have been applied to treat PSD, however, the long-term efficacy of these drugs is not ideal and there are many side effects. In the cognition of traditional Chinese medicine doctors, the main pathogenesis of PSD is stagnation of wind, fire, phlegm and blood stasis in the brain, coupled with poor mood, liver depression and qi stagnation disturbing the heart and brain, resulting in depression. According to the previous research [9], it was shown that fluoxetine combined with traditional Chinese medicine decoction that can clear phlegm and induce resuscitation, which has a significant effect on PSD patients. Besides, Geteng Tongluo capsule is a monomer plant medicine of total flavonoids of *Pueraria lobata*, which can activate qi and promote blood circulation, remove blood stasis and remove arthralgia, mainly treating the syndrome of phlegm and blood stasis blocking meridians and collaterals. In this study, the effects of Geteng Tongluo capsule combined with fluoxetine on the clinical efficacy, inflammatory factors and neurotransmitter levels of PSD patients were investigated, and the results showed that the combined treatment had a good effect.

NGF is a nerve growth factor, which contributes to the repair of nervous system injury, and its serum expression level is positively correlated with nervous

system function. Besides, being a specific marker of brain injury, S-100β protein located in astrocytes in the central nervous system, and the higher the level becomes, the more serious the nerve damage is. As for DA, a catecholamine neurotransmitter secreted by the brain, is able to promote the production of pleasure and excitement and the decrease of DA level is one of the key factors leading to depression [10]. The results of this study manifested that the total effective rate in observation group was significantly higher than that in control group. NGF and DA levels in the two groups were significantly enhanced after treatment, and NGF and DA levels in observation group were significantly higher than those in control group. Moreover, S100-β level, NIHSS and HAMD scores in two groups were significantly reduced after treatment, with those in observation group were significantly lower as compared with control group. It was suggested that Geteng Tongluo capsule combined with fluoxetine was helpful to relieve the depression of PSD patients, promote the recovery of their neurological function and regulate the level of neurotransmitters. In addition, 5-HT is released by the central nervous system before synapse, which is an important medium for regulating nerve activity. It acts on the brain to produce pleasant mood, and the decrease of its content is closely related to the occurrence of PSD. Furthermore, fluoxetine can inhibit the reuptake of 5-HT and increase the level of 5-HT, thus alleviating depression. Moreover, it can penetrate the brain barrier and directly act on the central system with a good effect. Additionally, the neurological deficit caused by insufficient cerebral blood flow is the main cause of PSD. The main component of Geteng Tongluo capsule, namely flavonoids, is the effective component of pueraria lobata, which has the effects of activating blood circulation, dredging collaterals, invigorating yang and relaxing tendons. Modern pharmacological research shows that [3] the total flavonoids from pueraria lobata can relax blood vessels, reduce blood viscosity and inhibit platelet aggregation. Besides, the total flavonoids of pueraria lobata have antioxidant capacity, which can scavenge oxygen free radicals, reduce the damage of oxidative stress to brain tissue and protect nerves.

Modern research shows that the high expression of inflammatory factors such as IL-1β, TNF-α and CRP will increase the depressive behavior of stroke patients, being an important role in the occurrence and development of PSD [1,11]. The results of this study manifested that the levels of IL-1β, TNF-α and CRP in the two groups patients were markedly reduced after treatment and the levels of IL-1β, TNF-α and CRP in observation group were significantly lower than those in control group. The reason may be that fluoxetine can regulate the level of neurotransmitters in the body to activate the anti-inflammatory pathway of vagus nerve, which played an anti-inflammatory role. At the same time, Geteng Tongluo capsule can reduce the level of peroxidation, alleviate the nerve inflammation, and inhibit the inflammatory reaction by down-regulating cell adhesion factor, matrix metalloprotein and other multi-targets, thus playing a role in protecting nerves [13-14]. Ting-ting Ma [7] et al. treated PSD patients with Geteng Tongluo capsule combined with paroxetine, and the results manifested that Geteng Tongluo capsule had a vital significant impact on PSD patients. That is, it was beneficial to reduce inflammatory reaction and enhance the neurological and cognitive functions of patients, which was consistent with the results of our study.

To sum up, Geteng Tongluo capsule combined with fluoxetine can effectively relieve the clinical symptoms, alleviate inflammatory reaction, increase the levels of neurotransmitters NGF and DA, reduce the level of S100-β, and relieve the depression of PSD patients.

Acknowledgement

Not applicable.

Conflict of Interest

The authors declare no conflicts of interest.

Author Contributions

Conceptualization, Data curation and Writing-Original draft, Z.Y.S; Writing-review and editing, H.H; 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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