DOI: 10.53469/jcmp.2025.07(08).22

Research Progress of Traditional Chinese Medicine in the Treatment of Post-stroke Insomnia

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Abstract: ***Stroke is the leading cause of death and disability in adults in China. It has the characteristics of high morbidity, high disability rate, high mortality, high recurrence rate and high economic burden. Post-stroke insomnia (PSI), as one of its complications, seriously affects the rehabilitation and quality of life of stroke patients. Traditional Chinese medicine has unique theoretical and practical advantages in the prevention and treatment of PSI, which can significantly improve the sleep structure and sleep quality of patients. It has been widely used in the treatment of post-stroke insomnia in clinical practice. This article systematically reviews the research progress of traditional Chinese medicine in the treatment of PSI in recent years, and discusses the future development direction in combination with clinical and cutting-edge technology applications, in order to provide reference for clinical practice and research of PSI.***

Keywords: Traditional Chinese medicine, Post-stroke insomnia, Summary.

1. Introduction

Post-stroke insomnia (PSI) is a common complication after stroke. It is not only a risk factor for stroke, but also aggravates neurological impairment, reduces quality of life, and increases the risk of death [1]. A study in China shows that the incidence of insomnia after stroke is very high, which can reach 57.1% [2]. At present, western medicine treatment of PSI mainly depends on oral drug therapy, mainly benzodiazepine receptor agonists. The short-term efficacy of drug treatment for insomnia has been confirmed by clinical trials, but long-term application still needs to bear potential risks such as adverse drug reactions and addiction. Traditional Chinese medicine is more and more widely used in the treatment of PSI because of its low price, small side effects, remarkable effect and simplicity. In the treatment of PSI, oral drugs are mainly traditional Chinese medicine compound, single drug and Chinese patent medicine. Traditional Chinese medicine emphasizes syndrome differentiation and treatment, and its individualized prescription can improve the clinical manifestations of patients. Modern Chinese patent medicine is also an effective way to meet the treatment needs because it is convenient to take and conducive to fast-paced life.

2. Chinese Herbal Compound

2.1 Chaihu Jia Longgu Muli Decoction

Chaihu Jia Longgu Muli Decoction is derived from the classic "Treatise on Febrile Diseases" of traditional Chinese medicine. It has the effects of calming the liver and suppressing yang, clearing heat and resolving phlegm, and calming the nerves. Modern studies have found that it can improve the sleep quality of patients by regulating central neurotransmitters, HPA and anti-inflammatory [3]. Fu Yanqiong [4] used Chaihu Jia Longgu Muli Decoction to treat PSI. The results showed that the scores of HAMD, HAMA and PSQI were significantly lower than those before treatment, and the effect was better than that of estazolam. It shows that Chaihu plus Longgu Muli Decoction can effectively improve the anxiety and depression symptoms of patients and improve the quality of sleep.

2.2 Huanglian Ejiao Decoction

"Huanglian Ejiao Decoction" was first recorded in Zhang Zhongjing's "Treatise on Febrile and Miscellaneous Diseases" in the Han Dynasty. It has the effects of nourishing yin and lowering fire, calming the nerves and removing trouble. The study found that Huanglian Ejiao Decoction can effectively improve the sleep structure, mainly by regulating the HPA axis, controlling the content of 5-HT, NE, DA and other central neurotransmitters, regulating intestinal flora, inhibiting inflammatory factors and other ways to improve the body's sleep behavior and prolong sleep time [5]. It was found that the addition and subtraction of Huanglian Ejiao Decoction had a significant effect on patients with insomnia of yin deficiency and fire excess syndrome after stroke, which could significantly improve the clinical symptoms and sleep quality of patientsIt was found that the addition and subtraction of Huanglian Ejiao Decoction had a significant effect on patients with insomnia of yin deficiency and fire excess syndrome after stroke, which could significantly improve the clinical symptoms and sleep quality of patients [6].

2.3 Tianwang Buxin Dan

Tianwang Buxin Dan has the effect of nourishing yin and clearing heat, nourishing blood and tranquilizing mind. Ma Xiaohan [7] found that Tianwang Buxin Dan had a significant improvement effect on post-stroke insomnia model rats. In this study, rats were divided into normal group, model group and Tianwang Buxin Dan low (1.9g/kg) and high (7.6g/kg) dose groups. After 7 days of intervention, it was found that compared with the model group, Tianwang Buxin Dan each dose group could effectively reduce the neurological deficit score (Zea-Longa score), shorten the sleep latency and prolong the sleep duration, and improve the sleep state. At the same time, it significantly improved the ability of learning and memory, which was manifested by shortening the escape latency in the Morris water maze positioning navigation experiment, increasing the number of crossing the original platform in the space exploration experiment, and increasing the new object recognition index. In terms of brain structure

and metabolism, Tianwang Buxin Dan intervention can reduce the area of cerebral infarction (T2WI imaging), regulate the level of metabolites in the hypothalamus area, reduce choline (Cho) and γ-aminobutyric acid (GABA), and significantly reduce myo-inositol (MI) in the high-dose group. In addition, Tianwang Buxin Dan could significantly reduce the levels of serum pro-inflammatory factors interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), and increase the level of anti-inflammatory factor interleukin-10 (IL-10). At the molecular level, it can up-regulate the expression of the circadian clock core protein / gene Bmal1 in the hypothalamus, and down-regulate the protein and gene expression of the microglia activation marker Iba1. In summary, Tianwang Buxin Dan can play a therapeutic role in insomnia after stroke by reducing neurological deficits, improving sleep disorders, enhancing learning and memory ability, reducing cerebral infarction area, regulating nerve metabolism, reducing inflammatory response, regulating circadian clock genes, and inhibiting microglia activation.

2.4 Da ChaiHu Decoction

Xiao Hongqin [8] randomly included 80 patients with insomnia after stroke into group A and group B, 40 cases each. Both groups were given routine basic treatment. Group A was additionally treated with estazolam tablets, and group B was additionally treated with modified Da chaihu Decoction. Both groups were treated for 2 weeks. The indexes of the two groups were compared. The results showed that after treatment, the effective rate of group A was 72. 5%, and that of group B was 90.0%. After treatment, the PSQI and FS-14 scores of group A and group B were lower than those before treatment, and the decrease of group B was greater than that of group A; after treatment, the SS-QOI score, serum 5-HT, BDNF and DA levels in group A and group B were higher than those before treatment, and the increase level in group B was higher than that in group A. It shows that the clinical efficacy of Dachaihu Decoction in the treatment of insomnia after stroke is definite, which can effectively improve the levels of 5-HT, BDNF and DA, and improve the sleep and life of patients.

2.5 Shugan Anmian Decoction

Jiang Yongqiu [9] with Shugan Anmian Decoction (Chaihu 15g, Chenpi 12g, Chuanxiong 10g, Xiangfu 6g, Zhiqiao 6g, Baishao 6g, Dangshen 20g, Huangqi 15g, Baizhu 10g, Danggui 10g, Longyanrou 10g, Fushen 20g, Yuanzhi 10g, Suanzaoren 20g, Gancao 3g, Dazao 3g) was used to treat post-stroke insomnia with liver depression and spleen deficiency. The results showed that Shugan Anmian Decoction was effective in treating post-stroke insomnia (liver depression and spleen deficiency syndrome). Clinical observation showed that the curative effect was better than that of alprazolam, with fewer side effects and high safety.

2.6 Chai Shao Long Mu Decoction

Zhao Dongzhi [10] treated PSI with Chaishao Longmu Decoction. Chaishao Longmu Decoction can effectively improve the sleep quality of insomnia patients with liver depression and blood deficiency syndrome after stroke, improve the quality of life, and reduce the content of serum orexin A may be one of its mechanisms.

2.7 Jiawei Xiaoyao Powder

In the study of Yu Liheng [11], 122 patients with PSI were randomly divided into experimental group (61patients, Jiawei Xiaoyao Powder combined with Baduanjin) and control group (61patients, estazolam tablets). The results showed that after treatment, the scores of PSQI and Fatigue Scale (FS-14) in the two groups were significantly decreased, the scores of SS-QOL and the levels of NPY were significantly increased, while the levels of serum substance P(SP) were significantly decreased. The experimental group was significantly better than the control group in improving PSQI, FS-14, SS-QOL scores, increasing NPY level and reducing SP level. In addition, the total effective rate of treatment in the experimental group was also significantly higher than that in the control group. This study shows that Jiawei Xiaoyao Powder combined with Baduanjin can effectively improve the sleep quality, fatigue and quality of life of patients with insomnia after stroke, and its clinical efficacy is better than that of conventional western medicine.

3. Chinese Medicine Single Drug

3.1 Akebiae Fructus

Akebiae Fructus has the effects of soothing liver and regulating qi, activating blood and relieving pain, resolving masses and diuresis. Liu Jingfeng [12] studied the therapeutic effect and mechanism of Akebia extract on post-stroke insomnia model rats. In this study, 60 SD rats were randomly divided into sham operation group, model group, positive control group (escitalopram, 10mg/kg), and Akebiae Fructus extract low, mediumand high dose groups (25,50,100 mg/kg). Except for the sham operation group, the post-stroke insomnia model was constructed in the other groups and verified by mNSS score. The results showed that compared with the sham operation group, the brain tissue of the model group showed pathological damage such as blurred boundary and lymphocyte infiltration, the escape latency of Morris water maze was significantly prolonged, the levels of serum pro-inflammatory factors TNF-α, IL-1β and IL-6 were significantly increased, and the mRNA and protein expression of key molecules (PI3K and Akt) of PI3K/Akt signaling pathway in brain tissue were significantly up-regulated. Compared with the model group, the above abnormal indexes of rats in each treatment group (including positive control group and each dose group of Akebiae Fructus) were significantly improved after intervention with Akebiae Fructus extract or escitalopram. The pathological damage of brain tissue was alleviated, the escape latency was shortened, the levels of serum TNF-α, IL-1βand IL-6 were decreased, and the mRNA and protein expressions of PI3 K and Akt in brain tissue were down-regulated, the improvement effect of the extract group was dose-dependent. It is worth noting that the high-dose group of Anemarrhenae has the same effect as the positive control group (escitalopram) in improving the above indicators (the difference is not statistically significant), while the effect of the low-dose group is weaker than the positive control group. This study showed that Akebiae Fructus extract, especially high dose (100mg/kg), could

effectively improve the learning and memory dysfunction and pathological damage of brain tissue in post-stroke insomnia model rats by inhibiting over-activated PI3K/Akt signaling pathway and reducing inflammatory response (reducing TNF-α, IL-1β, IL-6).

3.2 Spine Date Seed

Spine Date Seed has the effects of tranquilizing the mind, nourishing the heart and tonifying the liver, generating fluid and stopping thirst, and astringing sweat. Modern pharmacological studies have found that Spine Date Seed contains triterpenoid saponins, flavonoids, alkaloids, fatty acids and other chemical components, with sedative and hypnotic, anticonvulsant, antidepressant, anti-anxiety, anti-arrhythmia, anti-myocardial ischemia, anti-inflammatory, anti-oxidation, anti-tumor, improve learning and memory ability and other effects [13]. The mechanism of Spine Date Seed in the treatment of post-stroke insomnia is mainly to inhibit inflammation, regulate neurotransmitters (including 5-HT, NE, DA, GABA, etc.), and regulate HPA axis function [14]. Zhao Cui [15] found that the indexes of TNF-α, IL-1β, IL-6 and IL-2 in the model group were significantly increased by using the extract of Spine Date Seed to intervene in sleep deprivation rats, indicating that sleep deprivation led to the disorder of immune function in rats, which made them in a state of stress, and the index of inflammatory factors in serum increased. After the intervention of Spine Date Seed extract, the index of inflammation decreased significantly, indicating that Spine Date Seed could inhibit the release of inflammatory factors by regulating the balance of lymphocyte subsets, so as to improve the immune dysfunction caused by sleep deprivation and relieve insomnia symptoms. Lu Fang [16] intervened in hemorrhagic stroke rats by total saponins of Spine Date Seed. After intervention, compared with the control group, GABA positive neurons in the treatment group were significantly reduced, indicating that total saponins of Spine Date Seed could inhibit NMDA receptor, reduce the depolarization of Glu and GABA in postsynaptic neurons, and inhibit the release of glutamate excitotoxicity, so as to protect neurons and improve the behavioral changes of stroke rats. Hua Yue [17] caused a rat model of insomnia by intraperitoneal injection of p-chlorophenylalanine, and then gave the extract of Spine Date Seed. Finally, it was found that the extract of Spine Date Seed could down-regulate the levels of CRH, ACTH and CORT by regulating the HPA axis, and increase the expression of serum IL-1β and TNF-α to improve insomnia symptoms and abnormal behavior of rats caused by insomnia.

4. Chinese Patent Medicine

4.1 WuLing Capsule

The main component of Wuling capsule is Wuling fungus, which is a strain isolated from the traditional Chinese medicine Wuling ginseng. Wuling ginseng is one of the classic sedative drugs in traditional Chinese medicine. Traditional Chinese medicine believes that it has sweet taste, flat nature, and has many effects such as tranquilization and hemostasis. Wuling capsule has the effect of tonifying kidney and brain, nourishing heart and tranquilizing mind. Chen Qiuxia [18] selected 64 patients with insomnia after stroke as the observation objects, and divided them into control group and observation group according to the random number table method. 32 cases in the control group were treated with zopiclone, and 32 cases in the observation group were treated with zopiclone combined with Wuling capsule. The clinical efficacy, NIHSS, SF-36, PSQI, 5-HT, brain-derived neurotrophic factor (BDNF) and incidence of adverse reactions were compared between the two groups. The results showed that the total effective rate of the observation group was higher than that of the control group, and the NIHSS and PSQI scores of the two groups decreased and the SF-36 score increased after treatment. The NIHSS and PSQI scores of the observation group were lower than those of the control group, and the SF-36 score was higher than that of the control group. After treatment, the levels of BDNF and 5-HT in the two groups increased, and those in the observation group were higher than the control group. It shows that Wuling capsule is effective in the treatment of PSI. It can effectively improve the symptoms of stroke, improve the quality of sleep and quality of life, and has high safety.

4.2 PeiYuan TongNao JiaoNang

PeiYuanTongNao JiaoNang contains tortoise shell, cartialgenous, earthworm, scorpion and other traditional Chinese medicine components, which has the function of dredging meridians. Efficacy of activating collaterals, tonifying kidney and filling essence. Li Dan [19] randomly divided 86 patients with post-stroke depression and insomnia into two groups. The control group (43 cases) only received repetitive transcranial magnetic stimulation, and the observation group (43 cases) was treated with PeiYuan TongNao JiaoNang on the basis of magnetic stimulation for 1 month. The results showed that the total effective rate of the observation group (95. 35%) was significantly higher than that of the control group (76. 74 %). The observation group was superior to the control group in improving the depressive symptoms of the HAMD scale (anxiety, despair, block, day and night changes, sleep disorders, cognitive disorders) and sleep quality indicators (improving sleep efficiency, shortening sleep latency, reducing the number of awakenings, and prolonging the total sleep time). At the same time, the observation group had more advantages in reducing serum SP levels and increasing serum NPY and DA levels. There was no significant difference in the incidence of adverse reactions between the two groups. It shows that PeiYuan TongNao JiaoNang can effectively alleviate depressive symptoms, improve sleep and regulate related neurotransmitter levels.

5. Summary

PSI significantly affects the rehabilitation process and quality of life of patients. With its unique advantages of overall regulation and syndrome differentiation, traditional Chinese medicine treatment has good overall safety and relatively few side effects, showing a good application prospect. The core treatment idea is to reconcile qi and blood yin and yang, tranquilize the mind. At present, the research focuses on the application and therapeutic mechanism of traditional Chinese medicine compound, traditional Chinese medicine single drug and Chinese patent medicine. Modern studies have shown that these drugs may play a role in regulating sleep by regulating the levels of neurotransmitters such as 5-HT and GABA,

inhibiting excessive inflammatory response, and regulating the function of hypothalamic-pituitary-adrenal (HPA) axis. However, limitations still exist, such as the small sample size of most clinical studies, the lack of late follow-up of patients, which makes it difficult to determine the long-term efficacy, and the lack of objective indicators when evaluating the improvement of insomnia. Future research needs to further confirm its efficacy through large-sample, high-quality randomized controlled trials, further clarify the specific targets and material basis, and explore standardized medication regimens, in order to provide safer and more effective treatment options for PSI patients.

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