

Research Progress on the Mechanism of Fuyuan Xingnao Decoction in the Treatment of Acute Ischemic Stroke

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Abstract: Stroke is the leading cause of death and disability in Chinese residents, and acute ischemic stroke accounts for about 80% of all stroke types. Its disability and death rate have been high for many years. Therefore, actively exploring its pathogenesis and in-depth study of its effective prevention and treatment methods have become a major medical topic of great scientific significance and social value. Fuyuan Xingnao Decoction is a traditional Chinese medicine compound created under the guidance of the traditional Chinese medicine theory "Fuyuan Xingnao Method". It is clinically used in the treatment of acute ischemic stroke and has significant therapeutic effect, which can improve the protection of blood-brain barrier, anti-atherosclerosis, promote angiogenesis, improve nerve function, anti-coagulation and anti-platelet aggregation. By collating, summarizing and analyzing a large number of relevant literatures, the mechanism of Fuyuan Xingnao Decoction in the treatment of acute ischemic stroke was reviewed, in order to provide scientific theoretical basis for the treatment of ischemic stroke-related diseases with Fuyuan Xingnao Decoction as the starting point.

Keywords: Acute ischemic stroke; Fuyuan Xingnao decoction; Mechanism of action

1. Introduction

The latest global Burden of disease study of the Brain Prevention Commission of the National Health Commission shows that ^[1], the overall lifetime risk of stroke in China is 39.9%, ranking first in the world, indicating that about 2 out of every 5 people will suffer from stroke in their lifetime, and China has become the country with the highest lifetime risk of stroke in the world ^[2]. With the widespread prevalence of stroke risk factors, the burden of stroke disease in China will increase explosively in the future ^[3-4]. The Lancet, an authoritative international journal, published online the results of the 2017 study on the burden of disease in China, which was completed by the Chinese Center for Disease Control and Prevention, the Chinese Center for Chronic Noncommunicable Disease Prevention and Control, and the Institute for Health Measurement and Evaluation of the University of Washington. Studies have shown that from 1990 to 2017, the disease spectrum of Chinese residents has undergone major changes, and stroke and ischemic heart disease have replaced lower respiratory tract infections and neonatal diseases as the main causes of disease burden ^[5]. In 2019, the incidence, morbidity and death of stroke in China were 3,935,200, 28,760,200 and 2,189,200, respectively, and the disability-adjusted life years (DALY) caused by stroke were 45.991 million years, mainly years of life lost from premature death (YLL) (86.79%). The highest rate of YLD was ischemic stroke (IS), followed by intracranial hemorrhage (ICH). The overall disease burden of IS was similar to ICH, and both were much higher than subarachnoid hemorrhage (SAH). The burden of disease increases with age ^[6]. Acute ischemic stroke (acute ischemic stroke, AIS) belongs to the "stroke" of traditional Chinese medicine. A large number of ancient books and literatures record that stroke involves multiple viscera and has a wide impact on the human body.

Currently, there are many studies on Fuyuan Xingnao Decoction in the treatment of AIS, but the studies mainly focus on the observation of efficacy and single mechanism of action. The in-depth study and summary of it are still lacking. Therefore, this paper reviews the understanding of AIS in traditional Chinese medicine and the mechanism of action of Fuyuan Xingnao Decoction in the treatment of acute ischemic stroke by consulting and sorting out relevant domestic literature, in order to provide services for further clinical treatment of AIS.

2. Traceability of Fuyuan Xingnao Decoction

In AIS, Zhang Zhongjing of the Han Dynasty put forward the name of "apoplexy" for the first time in his "Synopsis of Golden Chamber · History of Apoplexy Disease and Its Pathogenesis and Treatment", and discussed in detail the main symptoms, signs and pathogenesis of the disease. Since then, the disease of sudden fainting, hemiplegia, astringent speech, mouth and eye askew syndrome as the main disease was named "stroke disease". As early as in the Huangdi Neijing period, the symptoms and signs of "stroke" were described, and the contents were scattered in the records of diseases such as "big jue", "pouncing", "Yaqu", "body deviation" and "Fengfei". In the later dynasties, according to the etiology, pathogenesis and pathogenesis of the disease, the Chinese medical scientists continued to describe it succinctly and graphically, and drew up a variety of disease names. Until the famous doctor Zhang Xichun in the Republic of China in the "Medical ZhongzhongShenxilu" first clearly divided the disease into "cerebral anemia syndrome" and "cerebral congestion syndrome", belonging to the western medicine "cerebral infarction" and "cerebral hemorrhage"; The Term of TCM Clinical Diagnosis and Treatment issued by the State Bureau of Technical Supervision in 1997 officially divided stroke into two types: ischemic and hemorrhagic. "Disease cause pulse treatment" recorded "hemiplegia cause, or qi coagulation stagnation, pulse arthralgia, or stomach heat generating phlegm, flow into the channel." "Medical Zhong Shen Xilu" pointed out: "Qi and blood deficiency, its meridians more stasis... To use the blood products, in order to relieve its stasis, then withered, flaccidity of the disabled self healing." "Only by removing blood stasis in the brain can it work." It can be seen that due to qi deficiency, blood flow stops, Qi can not be done, blood can not honor, Qi and blood stasis, vein impediment, and limb paralysis can not be used. Therefore, the application of supplementing qi and activating blood therapy is extremely important. The influence of apoplexy disease is extensive, which has been deeply understood by ancient people, and provides a rich theoretical basis for modern doctors to study AIS.

The theory of Fuyuan Xingnao decoction treating acute ischemic apoplexy is based on the syndrome that apoplexy is the primary deficiency and the deficiency of qi and blood, and wind, fire, phlegm, qi and stasis are the symptoms. The acute stage is dominated by standard hyperplasia, which is manifested as mutual causation and interlocking of pathological factors such as wind, fire, phlegm and blood stasis [7,8]. As the "spiritual pivot" says, "the true qi goes away, and the evil qi stays alone." Zhang Zhongjing thinks that "the veins are empty", and Wang Qingren's "Medical Forest Correction of mistakes on Hemiplegia" says that "hemiplegia, loss of vitality, is its source". Deficiency of Yin blood or aging body, deficiency of liver and kidney, excess liver-yang, improper rest and rest, resulting in Yin deficiency Yang hyperactivity, Qi and blood on the reverse, Mengshen Qi; Or lack of Qi and blood, vein emptiness, wind evil, qi and blood obstruction; Or phlegm wet xin sheng, shape sheng qi failure, external wind induces internal wind, phlegm wet blocked meridians, sudden disease. "Fuyuan Xingnao Decoction" is based on the academic experience of Professor Hu Jianhua, the late national famous traditional Chinese medicine professor of Longhua Hospital affiliated to Shanghai University of Traditional Chinese Medicine, aiming at the disease mechanism of "healthy qi deficiency, phlegm and blood stasis, wind and fire fanning", taking the main support of vitality, with the method of expelling phlegm and removing blood stasis, relieving heat and wind, awakening brain and opening the body, and establishing Fuyuan Xingnao Decoction.

Professor Fang believes that the pathogenesis of AIS is mainly based on "yuan qi deficiency", and the core pathogenesis is phlegm-stasis interformation and phlegm-heat generation of wind [9]. The proposed TCM compound Fuyuan Xingnao Decoction is composed of Cottonopsis, notoginseng, calamus, araceae, leechi, rhubarb, Leonurus and other drugs, which can be used together to restore yuan and awake brain, remove blood stasis and dissipate phlegm, and relieve heat and wind [10]. Codonshen tonifying spleen and supplementing lung is the king, Fuzheng curing the root, making lung Qi Xuanchang, temper healthy transport, then Qi and blood exuberant, phlegm and dampness from itself, so that Qi blood line, then blood stasis self-elimination; Shichao phlegm to clear the opening, Notoginseng activating blood stasis, leech breaking blood stasis, respectively for phlegm dampness, blood stasis of the evil effects, and Shichao, notoginseng mild, but also to prevent bitter cold too much, healthy qi damage; Rhubarb clear heat and detoxify, Tongfu and diarrhea, and can promote blood circulation and remove blood stasis; Arisaema removes wind phlegm, removes dampness phlegm, and can dispel wind and calm panic; Motherwort promotes blood and benefits water, taking into account the evil of "phlegm and stasis". Combined use of all kinds of drugs, xin open bitter down, cold and warm combined, playing a total of recovery and awakening brain, eliminating stasis and eliminating phlegm, heat and wind.

A large number of clinical and basic experimental studies have proved that Fuyuan Xingnao Decoction can intervene in the process of AIS through multiple mechanisms of action, such as protecting the blood-brain barrier, anti-atherosclerosis, promoting angiogenesis, improving nerve function, anti-

coagulation and anti-platelet aggregation, and has significant clinical efficacy in the treatment of cerebral infarction disease, so it has long-term value of in-depth research. The research progress of its mechanism of action in the treatment of AIS is summarized below.

3. Mechanism of action of Fuyuan Xingnao Decoction in treating AIS

3.1. Protection of blood-brain barrier

The blood-brain barrier mainly refers to a function formed by the whole neurovascular unit, which is mainly a semi-permeable membrane formed through the interconnection and interaction of non-cellular matrix and cell matrix in the neurovascular unit, and it can participate in the regulation and maintenance of brain operation [11]. The blood-brain barrier is the first barrier for blood to enter the brain tissue, and endothelial cells are its core components, which have relatively special molecular and structural characteristics. Experimental studies have shown that Fuyuan Xingnao Decoction can effectively protect the blood-brain barrier, reduce the secondary damage caused by reperfusion injury, reduce the permeability of the blood-brain barrier, reduce the progression of brain edema, reduce the swelling degree of cortical nerve cells, inflammatory cell infiltration and microvascular endothelial cell damage, and then improve nerve defect behavior. Promote the regeneration of local nerves and blood vessels and the establishment of collateral circulation [12-19].

3.2. Anti-atherosclerosis

Atherosclerosis (AS) is a general term for a series of lesions such as local plaque thickening of the intima of arteries, which eventually leads to reduced elasticity of the blood vessel wall and stenosis of the lumen [20]. AS is a chronic vascular inflammatory disease, which is easy to develop into ischemic heart disease, stroke and other peripheral artery diseases, and is also one of the diseases with a high mortality and disability rate worldwide [21]. In the theoretical system of traditional Chinese medicine, it is considered to belong to the categories of "pulse impediment", "stroke" and "vertigo" [22]. It has been suggested that the root cause is the deficiency of blood stasis [22] and the "unfavorable channel" [23]. Fang Lingyun [24] randomly divided 80 patients with wind-phlegm and blood-stasis cerebral infarction into control group and observation group. The observation group was given Fuyuan Xingnao Decoction orally for 4 weeks on the basis of the control group. To observe the effects of Fuyuan Xingnao Decoction on the levels of oxidized low density lipoprotein (ox-LDL), interleukin-18 (IL-18), lipoprotein-associated phospholipase A2 (Lp-PLA2) and carotid atherosclerosis plaque in patients with cerebral infarction with wind phlegm and blood stasis.

The results showed that Fuyuan Xingnao decoction could improve the symptoms of nerve defect, improve the ability of daily living, and inhibit the formation of carotid atherosclerosis plaque in patients with wind-phlegm-stasis cerebral infarction.

3.3. Promotion of angiogenesis

The treatment of stroke is to reconstruct the collateral channels after infarction. Cerebrovascular reconstruction is divided into three processes, namely, angiogenesis, arteriogenesis and arteriogenesis, and cerebrovascular reconstruction mainly depends on angiogenesis [25]. Angiogenesis is a physiological process by which microvessels branch from pre-existing blood vessels. After ischemic stroke, the blood-brain barrier (BBB) is severely damaged, leading to increased degree of secondary brain injury edema, leading to infiltration of peripheral immune cells and exacerbating the inflammatory response of the central nervous system (CNS) [26]. Cumulative evidence suggests that angiogenesis not only alleviates BBB leakage, but also contributes to neuronal metabolism and remodeling [27-28]. Sun Lihua et al. studied rats and found that after treatment in the Fuyuan Xingnao decoction group, the number of new blood vessels in ischemic area of rats with diabetic cerebral infarction increased, the blood vessel wall was more complete, and the blood vessel diameter thickened significantly than that in the control group. Fuyuan Xingnao Decoction can improve blood glucose, up-regulate the expression of CD31 in vascular endothelium, promote angiogenesis, improve the ultrastructure of cerebral microvessels, improve blood glucose and Bederson score of rats, indicating that Fuyuan Xingnao Decoction has the effect of promoting angiogenesis and repair of blood vessels and nerves, promoting angiogenesis of infarct tissue area, and improving brain microcirculation [29-30]. Wang Liping [31] studied 90 patients with lacunar cerebral infarction and found that Fuyuan Xingnao Decoction combined with Western medicine had better efficacy in the treatment of lacunar cerebral infarction, which could reduce the degree of nerve function

injury, improve the ability of daily living, improve the compliance of large blood vessel wall, improve blood vessel elasticity, inhibit the body's inflammatory response, and reduce the toxic effect of NO on nerve cells.

3.4. Improving Nerve function

A few hours after AIS occurs, axon damage leads to abnormal signal transmission between neurons and between cortical and sub-cortical centers, and the connection established between nerve cells is interrupted, so patients often suffer from stroke sequelae such as limb, language and cognitive dysfunction after the disease is relieved [32-33]. Therefore, improving the neurological function of AIS patients is the key to the rehabilitation of patients. Nerve cell protection therapy is an important means to treat ischemic stroke. Compared with the strict time window and serious complications of thrombolytic therapy, neuroprotective therapy in the early stage of acute ischemic stroke has a better effect. Neuroprotective agents can reduce ischemic injury of brain tissue and protect peripheral nerve cells in infarction area by blocking all links of ischemic cascade reaction, thus achieving therapeutic effect [34]. Chen Zhenyi et al. [35] conducted clinical observation on 192 patients with acute cerebral infarction and found that the degree of neurological impairment and daily living ability of patients in the Fuyuan Xingnao method group was significantly improved after treatment compared with that before treatment, and the experimental group was significantly improved compared with the control group. Meng Xiuyan [36] found that Fuyuan Xingnao Decoction could significantly enhance the expression of VEGF in the brain tissue of rats with diabetes mellitus complicated with cerebral infarction, and promote the recovery of nerve function. Huang Jinyang et al. [37] confirmed that the rats in the DMCI model group showed obvious neurological sign defects and significantly decreased activity ability after surgery. After treatment with Fuyuan Xingnao Decoction, the behavioral sign scores of the model group with neurological defects increased compared with the sham operation group, the diabetes group and the normal group. Compared with the model group, the nerve defects were significantly improved in the treatment group. Geng Yun [38] treated patients with acute ischemic stroke and experimental group with Fuyuan Xingnao Decoction on the basis of conventional Western medicine treatment in stroke guidelines. Results After treatment, NIHSS score and disease diagnosis score of both groups decreased, while BI increased. The results showed that Fuyuan Xingnao decoction combined with conventional western medicine treatment can better improve the neurological impairment of patients with acute ischemic stroke, improve the ability of daily living, reduce the severity of the disease, and contribute to the improvement of the disease and improve the curative effect. He Shaohua et al. [39-40] found that after Fuyuan Xingnao Decoction was injected into DMCI rats, the proteins of SDF-1, CXCR4 and VEGF in brain tissue were significantly increased, indicating that Fuyuan Xingnao decoction could promote the regeneration of local blood vessels and nerves, accelerate the recovery of nerve function, and then improve the endothelial function of damaged blood vessels to treat DMCI. Wang Aili [41] found through clinical studies that adding Fuyuan Xingnao Decoction to basic treatment for patients with acute cerebral infarction could significantly improve hemorheology indexes and nerve function, and improve therapeutic effect.

3.5. Anticoagulation and antiplatelet aggregation

Normal platelets in the blood participate in the clotting process of the body, but when stimulated by inducers adenosine diphosphate and arachidonic acid, platelets are activated and their adhesion and aggregation are enhanced, which may lead to thrombosis [42]. Antiplatelet therapy is an effective method to treat acute stage of ischemic stroke. The application of drugs that inhibit anti-platelet aggregation can prevent blood coagulation in blood vessels and reduce the occurrence of cerebrovascular coagulation and stasis [43]. Chen Jimin et al. [44] studied patients in the convalescent stage of ischemic stroke and adopted Fuyuan Xingnao Decoction for treatment on the basis of the control group, showing that Fuyuan Xingnao Decoction can effectively improve the coagulation function and endothelial function of patients, reduce the score of traditional Chinese medicine symptoms. And it can improve life ability, with significant therapeutic effect and good prognosis. Zhuang Daiwa [45] adopted Fuyuan Xingnao Decoction combined with conventional Western medicine therapy to treat acute cerebral infarction (wind phlegm and blood stasis syndrome), the use of Fuyuan Xingnao decoction combined with conventional Western medicine therapy to treat acute cerebral infarction has significant effect, which can reduce the blood hypercoagulability of patients, promote blood circulation, improve the blood oxygen balance of patients, improve the quality of life of patients, and help patients recover. Chen Zhenyi et al. [46] conducted clinical observation on patients with acute cerebral infarction with Fuyuan Xingnao method, and found that the degree of neurological impairment and daily living ability of patients with Fuyuan Xingnao method were

significantly improved after treatment compared with that before treatment, and the experimental group was significantly improved compared with the control group. The results showed that Fuyuan and waking brain could improve the hypercoagulability of patients. It was found that Fuyuan Xingnao Decoction combined with conventional western medicine treatment can better improve the function of coagulation factor, fibrinogen and platelet in patients with acute cerebral infarction (wind-phlegm-stasis syndrome), reduce the content of D-dimer, thus improving the hypercoagulable state of patients, balancing the function of coagulation and fibrinolysis system, improving the neurological function of patients with cerebral infarction, and improving the condition of patients with cerebral infarction. Therefore, the mechanism of Fuyuan Xingnao Decoction may be related to the function of anti-platelet aggregation and balancing coagulation and fibrinolysis system.

4. Summary

In summary, there is a scientific basis for the treatment of AIS with Fuyuan Xingnao Decoction based on syndrome differentiation. Modern pharmacological and clinical studies have shown that Fuyuan Xingnao Decoction has a comprehensive effect of multiple components, multiple pathways and multiple targets in the treatment of AIS, which can protect the blood-brain barrier, reduce the permeability of the blood-brain barrier, reduce the progression of cerebral edema, and improve ischemic penumbra microcirculation. The pathological changes such as inflammatory infiltration, apoptosis and necrosis of ischemic brain tissue were improved. It can improve the symptoms of nerve defect, improve the ability of daily living, and inhibit the formation of carotid atherosclerotic plaque. It can increase the expression of SDF-1 and VAGF in brain tissue, decrease ET-1, enhance the release of NO reserve, improve endothelial diastolic function, regulate the generation of vascular endothelial cells, promote local vascular and nerve regeneration, and improve nerve function. To improve the quality of clinical prognosis; It can prevent platelet aggregation, balance the function of coagulation and fibrinolytic system, improve the hypercoagulability of patients, and play a positive role in promoting the recovery of nerve function of patients and improving the condition of patients with ischemic stroke^[47-49], which provides data and theoretical support for Chinese medicine scholars to study the target and mechanism of regulating AIS. However, there are still many mechanisms that are not clear and need to be explored. There are also some problems worth thinking about in the research. Since the pathogenesis of cerebral ischemia is complex and diverse, the research on the prevention and treatment of Chinese medicine should start from the characteristics of Chinese medicine, treat people as a whole, combine the holistic concept of Chinese medicine, and conduct the research on acute ischemic stroke based on syndrome differentiation. From a global perspective, stroke specialists in many hospitals systematically collate and analyze the data, and use modern statistical methods to summarize the different dose-effect relationships of different prescriptions and integrated Chinese and western medicine in the treatment of acute ischemic stroke. The principle of randomization, double blindness and control should be adopted in the research, which is very important for the summary of clinical experience and basic experimental research in the future. Ischemic stroke has the characteristics of rapid onset, rapid change and severe disease, and ultra-early treatment is particularly important.

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