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Advances in Research on Astragalus and Cinnamon Twig Five-Substance Decoction for Qi Deficiency and Collateral Stasis Type Diabetic Peripheral Neuropathy

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Abstract: ***Diabetic peripheral neuropathy (DPN) is one of the common complications of diabetes. The pain, numbness and sensory impairment caused by nerve damage are the main clinical manifestations, which seriously affect the quality of life of patients. According to traditional Chinese medicine, the pathogenesis of DPN is mainly qi deficiency, collaterals and blood stasis, and the basic principle should be invigorating qi, promoting blood circulation and dredging collaterals. As a classic prescription, Astragalus and Cinnamon Twig Five-Substance Decoction (ACTFSD) has remarkable effect in improving qi deficiency, collateral and blood stasis. In recent years, studies have shown that the decoction can effectively relieve the symptoms of diabetic peripheral neuropathy and improve the neurological function through multiple ways and multiple targets. This paper summarizes the research progress and action mechanism of DPN in the treatment of qi deficiency and collateral stasis, in order to provide reference for its clinical application and further research.***

Keywords: Diabetic peripheral neuropathy, Qi deficiency and collateral stasis, Astragalus and Cinnamon Twig Five-Substance Decoction, Clinical research, Review**.**

1. Introduction

With the aging population, the prevalence of diabetes has been rising, and the latest data show that about 536.6 million people have diabetes worldwide, with a prevalence of 10.5%. The number of people is expected to reach 783.2 million by 2045, with a prevalence of 12.2% [1]. While about 50% of people with diabetes develop DPN [2]. DPN is one of the most common chronic complications of diabetes, usually presenting with neurological symptoms such as numbness, tingling, sensory retardation or allergy in the hands and feet, which can lead to limb ulcers, infection and even amputation in severe cases [3]. Modern medicine believes that its pathogenesis is complex, involving abnormal glucose metabolism, oxidative stress, inflammatory response and microcirculation disorders [4]. Although western medicine treatment mainly focuses on blood glucose control, improvement of microcirculation, and application of nutritional nerve drugs, the efficacy is limited, and long-term drug use may bring adverse reactions.

The understanding of DPN in traditional Chinese medicine mostly belongs to the categories of “bi syndrome” and “gangrene”. The etiology and pathogenesis are mainly qi deficiency and collateral stasis, collaterals and pulse stasis, and the core treatment principles are invigorating qi and blood circulation, through meridians and activating collaterals. Astragalus cassia branch soup originated from the Synopsis of the Golden Chamber, which is composed of five medicines of astragalus, cassia branch, peony, ginger and jujube, and has the function of supplementing temperature, Yang and blood obstruction, and is used in the treatment of arthralgia and blood stasis syndrome [5]. In recent years, the application of Astragalus soup in DPN has attracted wide attention, and studies show that it has remarkable efficacy in improving pain, numbness and other symptoms and reducing nerve damage. This paper combines basic research and clinical research to review the research progress of ACTFSD in the treatment of qi deficiency and collateral stasis DPN.

2. Characteristics and Pharmacological Effects of ACTFSD

2.1 Formation Characteristics

ACTFSD consists of astragalus, cassia branch, peony, ginger and jujube, the prescription of each medicine is rigorous, together to fill the temperature of Yang, and blood obstruction. Astragalus can replenish qi and strengthen the surface, replenish qi and strengthen the body. As a prescription of Zhongjun medicine, it can improve the state of qi deficiency and enhance the bodys disease resistance. Guizhi can warm the cold, Yang qi, help the operation of qi and blood, improve the collateral stasis. Peony can nourish blood and camp, slow and urgent pain, with Guizhi can reconcile camp, relieve pain. Ginger can be warm and disperse cold, reconcile the spleen and stomach, help medicine into the meridian. Jujube can fill the qi, harmony camp wei. The whole prescription can play the comprehensive role of benefiting temperature, promoting blood circulation and dredging collaterals, which is suitable for arthralgia, numbness or pain caused by qi deficiency, collaterals and blood stasis.

2.2 Pharmacological Action

In traditional Chinese medicine, there is no name of DPN, and according to its symptoms such as numbness and pain, it can be attributed to the categories of "bi syndrome", "pain syndrome" and "gangrene" in traditional Chinese medicine. Ancient and ancient scholars summed up the pathogenesis of DPN as deficiency and blood stasis. Due to prolonged thirst, qi and Yin loss, Yin deficiency, Yin deficiency and heat endogenous, the essence dries up, resulting in blood gas stagnation and collateral obstruction, that is, qi deficiency and collateral stasis, which is the deficiency and solid, throughout DPN [6,7]. With the function of supplementing temperature, Yang and blood obstruction, the basic and clinical studies show that it has a good therapeutic effect on qi deficiency and collateral stasis type DPN.

An important mechanism of DPN with qi deficiency and collateral stasis is ischemia and hypoxia of nerve tissue caused by microangiopathy. Network pharmacology predicts anti-oxidation, anti-inflammatory, anti-cholinergic, and reduction of ER stress level [8]. Modern pharmacological studies show that Astragalus root and cassia branches can dilate blood vessels, improve the blood rheological indexes, and promote the blood supply of nerve tissue. The polysaccharide rich in Astragalus can regulate blood sugar; flavonoids in Astragalus have significant antioxidant effect, which can remove free radicals and reduce oxidative damage of nerve cells; the sol contained in cassia can relieve spasmodic and analgesia, dilate blood vessels and accelerate blood circulation [9,10]. White peony root extract may be a potential nerve growth promoting factor to promote neurite growth and peripheral nerve regeneration [11]. Ginger can promote the utilization of peripheral blood glucose, improve impaired hepatorenal glycolysis, and prevent gluconeogenesis, thus controlling tissue glycogen content [12]. Ginger contains 6-gingingolol and ginger extract can reduce blood sugar, can play anti-hyperalgesia and neuroprotective effect in mice with diabetic nerve pain [13]. Jujube extract was able to reduce the expression of proinflammatory factors IL-6, IL-1 β and TNF-α and improve neuropathic pain [14].

To sum up, ACTFSD can reduce blood sugar, improve neuronal function, reduce tissue pain, improve nerve blood supply, reduce nerve damage by improving microcirculation, anti-oxidation stress, anti-inflammation, and neurotransmitter regulation, preferably to achieve the effect of treating deficiency and blood stasis DPN.

3. Clinical Study on the Treatment of qi Deficiency and Collateral Stasis DPN in ACTFSD

3.1 Unilateral Efficacy Evaluation

ACTFSD has shown excellent clinical efficacy in the treatment of qi deficiency and collateral stasis DPN. This prescription can significantly improve the clinical symptoms of patients, such as limb numbness, pain, sensory abnormalities, and effectively relieve the discomfort of patients. At the same time, it can also significantly improve the nerve conduction velocity of the patients, including the motor and sensory conduction velocity of the median nerve and the peroneal nerve, thus bringing substantial improvement to the patients from the physiological function level. A clinical study on the treatment of DPN found that the total effective rate was 93.33%, the conduction velocity of sensory nerve and motor nerve was significantly improved, and the lower limb vibration sensory threshold was significantly reduced, which confirmed that the adjuvant treatment of DPN can improve the nerve conduction function of patients with DPN [15]. The clinical study of Hu Zonghua et al. found that fasting blood glucose, postprandial blood glucose, plasma viscosity and fibrinogen of patients were all lower than those of conventional western medicine treatment group, which proved that it could improve the blood glucose level of such patients and improve the quality of life of patients [16]. In addition, Astragalus soup can also significantly reduce the blood viscosity and fibrinogen level of patients, improve microcirculation disorders, and help to relieve the nerve ischemia and hypoxia caused by diabetes. Another clinical study used the self-before and after the control method, compared with before treatment, to improve the clinical symptoms of patients with microcirculation disorder [17]. As a traditional Chinese medicine compound, it has low side effects and high tolerance, providing a safe treatment option for patients with DPN. This prescription can not only significantly improve the clinical symptoms of patients, but also effectively improve the nerve conduction velocity, thus showing significant clinical efficacy in the treatment of DPN.

3.2 Exploration of the Combination Therapy Regimen

3.2.1 Combined nutritional nerve drugs: synergistic attenuation

The combination of ACTFSD and methocobalalamin can cooperate to improve nerve conduction function. A clinical study found that the total clinical symptom score (TCSS score) and tumor necrosis factor- α (TNF- α) were significantly lower than the control group, and the sensory nerve conduction velocity (SNCV) and MNCV) of the tibial nerve and median nerve were significantly higher than the control group. These results showed that acupoint injection in the treatment of DPN patients, which can effectively improve the nerve conduction velocity, reduce TNF- α level, and thus significantly improve the clinical symptoms of patients [18]. Another clinical study also confirmed that the combination of methecalamin with Astragalus and cassia chinensis was better to improve nerve conduction velocity [19]. The mechanism of action may be related to the improvement of microcirculation and the reduction of oxidative stress damage. In addition, combination therapy can also reduce the amount of methylocobalamin and reduce the incidence of gastrointestinal adverse effects caused by long-term use.

3.2.2 Combined metabolic regulators: to improve the microenvironment

The combination with lipoic acid can form the antioxidant synergistic effect. A clinical study in 96 cases confirmed that ACTFSD and taste combined lipoic acid treatment of DPN patients with TCM syndrome score, blood rheology index significantly lower, suggest ACTFSD and taste combined lipoic acid can reduce DPN qi deficiency syndrome, regulate

blood rheological index, improve the microcirculation [20]. Another study also confirmed that the treatment of combined with lipoic acid can significantly improve blood glucose and lipid levels and accelerate the nerve conduction speed [21]. Fan Shaoling et al. found that the combination of Astragalus and DPN can play multiple effects, significantly improve the coagulation function of patients, make patients better control dysfunction and improve the quality of life [22].

3.2.3 Combined with other therapies: multidimensional intervention

Astragalus and Cinnamon Twig Five-Substance Decoctio with other therapies can enhance the local efficacy. The clinical study results of Yang Lujie et al. found that the sensory nerve conduction velocity and motor nerve conduction velocity of the test group were higher than that of the control group, while the clinical symptoms (TCSS) score was lower than that of the control group. It proved that the effect of acupoint application was better with DPN [23]. Another study also confirmed that the combination of ACTFSD combined with meridian fluid injection method could better improve the nerve conduction function of patients [24]. Zou Pingping [18] People et al. also found that the combination of acupoint injection in patients with DPN was better. At the same time, the study also found that the combination of ACTFSD and negative pressure closed drainage treatment should treat diabetic foot, and the granulation time and wound healing time were shorter than the control, which indicates that the addition of ACTFSD combined with negative pressure closed drainage treatment should promote the wound healing of diabetic foot and improve the peripheral nerve function [25]. In Li Bolins clinical research, ACTFSD combined with hyperbaric oxygen therapy can improve the microcirculation of patients with DPN, rapidly increase oxygen and blood supply, and promote the recovery of nerve function [26]. In addition, ACTFSD combined with acupuncture for DPN also has good results. Zhao Rong et al. found that Astragalus and Cinnamon Twig Five-Substance Decoctio combined with warm acupuncture could effectively improve the clinical symptoms and signs of DPN patients with qi deficiency and collateral stasis, which was conducive to the recovery of nerve function and delay the progression of the disease [10]. Another clinical study also confirmed that the clinical effect of ACTFSD combined with acupuncture could effectively improve the numbness, pain, sensory abnormalities and other symptoms of DPN [27].

ACTFSD can improve microcirculation and repair damaged nerves through various mechanisms and multiple targets, so as to effectively alleviate clinical symptoms. In addition, when used in combination with other treatments, it can produce a synergistic effect, further promoting the improvement of clinical symptoms. At the same time, its safety is high, patients are generally easy to accept, and has a good application prospect.

4. Lack and Outlook

Although Astragalus and Cinnamon Twig Five-Substance Decoctio has shown good effect in the treatment of qi deficiency and collateral stasis DPN, there are still some problems to be solved. First, some clinical studies have small sample size and lack of multicenter and large sample randomized controlled trials, so the study design needs to be further standardized. Second, although some studies have revealed some of the mechanisms of action, the characteristics of its multi-pathway and multi-target effects still need to be further explored. Third, at present, it is mostly short-term efficacy observation, and there is a lack of research on the long-term prognosis of patients, so the long-term efficacy evaluation is very insufficient. Future studies should combine modern pharmacology and molecular biology techniques to further clarify the mechanism of action of WT, and conduct high-quality clinical studies to promote its application in DPN therapy.

5. Conclusion

As a traditional Chinese medicine compound, ACTFSD has shown a remarkable therapeutic effect on qi deficiency and collaterals and stasis DPN through its effects of invigorating qi and promoting blood circulation, warming meridians and dredging collaterals. This prescription has good potential in improving patients symptoms, enhancing neurological function and relieving microcirculatory disorders. Several studies have shown that the decoction can effectively reduce TCM syndrome in patients with DPN and regulate blood rheological indicators, thus improving microcirculation disorders. In addition, this formula has high safety and good tolerability, and with the deepening of research, The decoction is expected to become an important supplementary treatment for the treatment of DPN.

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