MEDS Chinese Medicine (2023)
Clausius Scientific Press, Canada

DOI: 10.23977/medcm.2023.051007
ISSN 2616-1753 Vol. 5 Num. 10

Research Progress of Buyang Huanwu Decoction in the Treatment of Diabetes Peripheral Neuropathy

Zhen Feng[1,a], Xuehua Han[1,b], Defen Wang[2,c,*]

[1]Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, 712046, China
[2]Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, 712000, China
[a]1006676094@qq.com, [b]1059388070@qq.com, [c]wangdefen69@sohu.com
[*]Corresponding author

Keywords: Diabetes; diabetes peripheral neuropathy; Buyang Huanwu Decoction

Abstract: Diabetes peripheral neuropathy (DNP) is a chronic complication of peripheral nerve injury caused by long-term onset of diabetes. In recent years, with the in-depth study of Chinese medicine in diabetes peripheral neuropathy, Buyang Huanwu Decoction has made some progress in its treatment. This article studies the mechanism and clinical efficacy of Buyang Huanwu Decoction on diabetes peripheral neuropathy, and provides a new method for the treatment of diabetes peripheral neuropathy.

1. Introduction

Diabetes peripheral neuropathy (DPN) is one of the most common chronic complications of diabetes, and its incidence can be as high as 25%~60% [1],, which is closely related to the course of diabetes, as shown in Figure 1. The longer the duration of illness, the higher the incidence, and vice versa. DPN patients have the most common distal symmetric polyneuropathy, with the most prominent clinical manifestations of numbness, tingling, and sensory abnormalities at the ends of the limbs, usually distributed in a glove or sock like manner, often involving the lower limbs, occurring symmetrically, with obvious nighttime symptoms [2], as shown in Figure 2. In severe cases, muscle atrophy, limb ulcers, gangrene, and other conditions may occur, and even amputation may occur [3]. This abnormality is the main cause of disability and death in diabetes patients [4]. Diabetes peripheral neuropathy covers a wide range. According to its clinical manifestations, it is equivalent to "blood arthralgia", "flaccidity syndrome", "syncope syndrome" and other syndromes secondary to diabetes [5]. The underlying cause of the disease is "deficiency in origin and excess in excess", which leads to blood stasis due to deficiency and the combination of deficiency and blood stasis. Buyang Huanwu Decoction was created by Wang Qingren of the Qing Dynasty and has the effect of tonifying qi, promoting blood circulation, and unblocking collaterals. It is a commonly used formula for qi deficiency and blood stasis, and plays an irreplaceable role in the treatment and prevention of DPN. This article expounds the etiology and pathogenesis of diabetes peripheral neuropathy, the mechanism of Buyang Huanwu Decoction in treating DPN and its clinical efficacy, which provides a reference for traditional Chinese medicine in treating diabetes peripheral neuropathy.

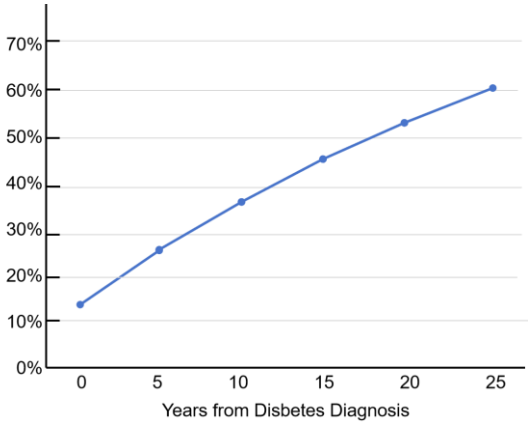

Figure 1: Incidence rate of DPN

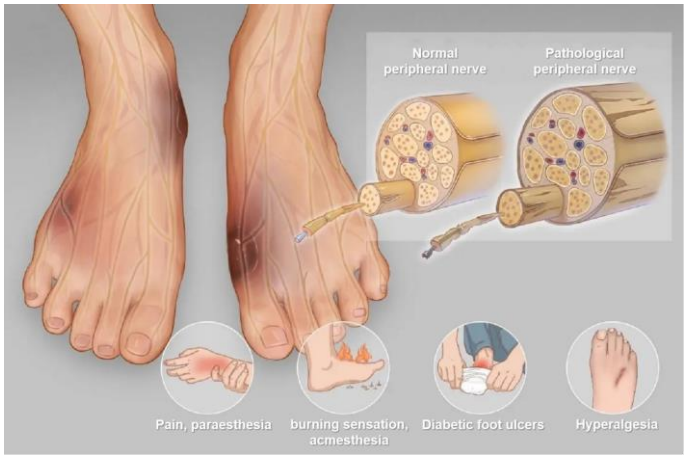

Figure 2: Symptoms of DPN

2. The therapeutic approach of Buyang Huanwu Decoction in treating DPN

2.1. Etiology and pathogenesis of diabetes peripheral neuropathy

DPN is a modern medical concept, which is not known in Traditional Chinese medicine. However, as one of the chronic complications of diabetes is developed on the basis of the prolonged treatment of diabetes and the prolonged course of the disease, its main clinical manifestations are numbness, coldness, pain and weakness of hands and feet. It should be classified as diabetes and "arthralgia syndrome", "blood arthralgia syndrome", "jue syndrome", "flaccidity syndrome" and other categories. According to the Huangdi Neijing, "fatty diet can cause internal heat, sweet diet can cause abdominal distension. Both of them can lead to spleen deficiency and counter-flowing Qi, resulting in Xiao Ke". Tt shows that the pathogenesis is mainly based on the body weakness, the deficiency of yin and dryness-heat. Diabetes patients with yin deficiency and dry heat burn for a long time, with prolonged illness entering the meridians and blood stasis blocking the veins.

With the development of modern medicine and the continuous deepening of its research, many doctors have proposed different understandings from different perspectives. The following is an example: Professor Zhou Shaohua [6] believes that the basic pathogenesis is "deficiency of yin and wei, prolonged illness damaging qi and blood", and treatment should focus on dispelling wind and unblocking collaterals, promoting blood circulation and resolving stasis, nourishing blood and blood. Professor Shao Jingming [7] believes that the etiology and pathogenesis of this disease are the prolonged consumption of thirst, damage to the normal qi, loss of qi, blood, yin and yang in the organs,

deficiency of spleen qi, endogenous dampness and turbidity, obstruction of phlegm and blood stasis, prolonged illness entering the meridians, and obstruction of muscles and meridians. Professor Zhou Desheng [8] believes that the basic pathogenesis of this disease is the deficiency of the five zang organs and the imbalance of yin and yang, and the key cause of diabetes peripheral neuropathy is the stagnation of meridians caused by the deficiency of qi and stagnation of prosperity and the stagnation of Xuanfu. Zhang Lu [8] believes that the pathogenesis of DPN is constantly evolving, with the disease initially characterized by yin deficiency or qi deficiency with blood stasis. As the disease progresses, it ultimately leads to both yin and yang being damaged with blood stasis. Dr. Pei Ruixia [9] believes that this disease is closely related to the liver, and its pathogenesis is a mixture of deficiency and excess. It is based on yin and blood deficiency, with qi stagnation, stasis, blood heat, phlegm dampness, and other criteria. The disease is located in the skin of striae, with the main lesion in the liver, closely related to the lungs, spleen, stomach, and kidneys.

Although doctors have different understanding and opinions on the pathogenesis of diabetes peripheral neuropathy, it is still not difficult to see they all believe that the nature of diabetes peripheral neuropathy is mostly based on deficiency and marked by excess.

2.2. Analysis of the Formula Meaning of Buyang Huanwu Decoction

Buyang Huanwu Decoction is a representative formula of the Qi Deficiency and Blood Stasis Theory created by Wang Qingren in the Qing Dynasty. It is composed of Huangqi, Danggui Wei, Chuanxiong, Taoren, Honghua, Chishao, and Dilong, as shown in Figure 3. In the formula, Huangqi is highly valued. Its sweet taste and warm nature enter the spleen and lung meridians, and it is used to greatly nourish the spleen and stomach qi. The aim is to "treat blood first by treating qi, and the circulation of qi leads to the circulation of blood"; Danggui, Chuanxiong, Red Peony, Peach Kernel, Safflower and other herbs are used together to promote blood circulation and eliminate stasis without harming the body; The earth dragon is good at regulating meridians and activating collaterals, and can be combined with various medicines to dispel blood stasis and unblock collaterals [10]. Throughout the entire recipe, supplementing qi can promote blood circulation, increasing qi can promote blood circulation, dispelling blood stasis without harming the right side, dispelling blood stasis without damaging the meridians, nourishing muscles and muscles, and healing all symptoms. The compatibility of this prescription is characterized by the extensive use of astragalus membranaceus. Animal experiments have shown that astragalus membranaceus has the functions of scavenging free radicals, protecting the activity of SOS enzyme, resisting lipid peroxidation, protecting the blood nerve barrier, preventing the formation of the internal lacunar septal syndrome of peripheral nerves, and protecting the peripheral nerve from ischemia-reperfusion injury [11].

Figure 3: Composition of Buyang Huanwu Decoction

3. Pathogenesis of diabetes peripheral neuropathy (DPN)

The pathogenesis of DPN is relatively complex and has not yet been fully elucidated. Persistent high glucose metabolism, Neurotrophin deficiency, oxidative stress, autoimmune diseases accompanied by glial cell activation are considered to be related to the pathogenesis of DPN [12], as shown in Figure 4.

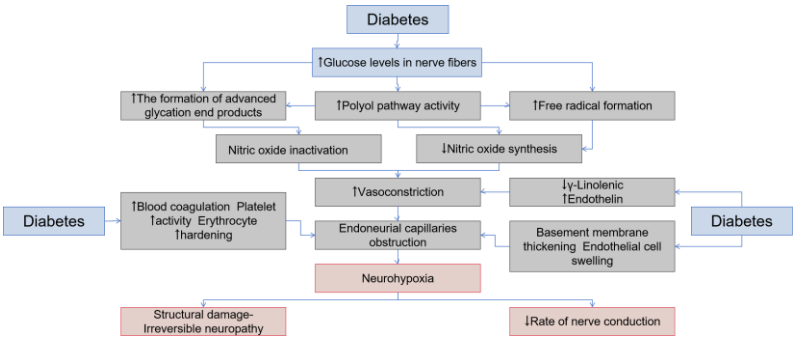

Figure 4: Pathogenesis of DPN

3.1. High glucose metabolism

High glucose metabolism is one of the main inducing factors of DPN caused by peripheral nerve injury. In the high glucose metabolic environment of diabetes patients, the peripheral nerve is vulnerable to damage, because the activity of Aldose reductase, the key enzyme involved in the polyol metabolism pathway, increases in the hyperglycemic state of the body, resulting in the massive accumulation of sorbitol and fructose in neurons, which cannot be effectively utilized and decomposed. It will lead to the increase and swelling of the Osmotic pressure in the cells, and in serious cases, it can lead to denaturation and necrosis [13], which will lead to the disorder of glucose metabolism, damage the function of vascular endothelial cells and cause the abnormality of nerve microcirculation, make the blood in a hypercoagulable state, narrow the vascular lumen, or even block, cause microcirculatory disorders, neurological ischemia and hypoxia damage, damage the continuity of the myelin sheath, and lead to neuropathy [14].

3.2. Deficiency of Neurotrophin

The lack of Neurotrophin is considered to be another important reason for inducing DPN [15]. Data shows that nerve growth factor, collagen Neurotrophin and Insulin-like growth factor in Neurotrophin participate in the occurrence and development of DPN. Studies have confirmed that Neurotrophin, as a special protein factor in the body, plays an important role in maintaining neurons and nerve fibers. The lack of Neurotrophin will lead to the decline of Nervous tissue physiological function and self-healing ability [16].

3.3. Oxidative stress

Oxidative stress is an imbalance between oxidation and antioxidant activity in the body, which is a negative effect of free radical production in the body. Due to the excessive peroxide product Malondialdehyde in the body of diabetes patients, the Superoxide dismutase that scavenges oxygen free radicals will be reduced. Starting the oxidative stress mechanism will lead to insulin resistance by interfering with insulin signal transmission and induce DPN [17]. On the one hand, oxidative stress leads to peripheral nerve damage and reduces the secretion of Neurotrophin; On the other hand,

sustained oxidative stress can induce nerve damage, even apoptosis, and correspondingly reduce intracellular neurotrophins, which in turn is not conducive to the body's self-compensatory repair of damaged nerves.

3.4. Autoimmune diseases with glial cell activation

In the case of continuous hyperglycemia, the anti-Nervous tissue antibody in the serum will destroy the patient's neurovascular barrier and cause autoimmune damage to the patient's Nervous tissue. Astrocyte can activate the differential subtype receptors of purine while releasing Adenosine triphosphate, increase the activity of Electrical synapse channel proteins to fully express them, and always play an important role in the occurrence and development of DPN [18].

4. The mechanism of action of Buyang Huanwu Decoction in treating DPN

4.1. Correcting metabolic disorders

The first choice for treatment of diabetes and DPN is to reduce blood sugar. Early intervention is given to diabetes patients. The better the effect of blood sugar control, the lower the possibility of inducing complications. Zhou Kaixuan [19] and others divided the diabetes animals successfully modeled into model control group, Metformin 0.2g/kg group, and Buyang Huanwu Decoction 12.6g/kg group. Each group was administered once, and various corresponding drugs were administered by gavage for 6 consecutive weeks. The results showed that the blood sugar, triacylglycerol, and cholesterol of diabetes animals were reduced, indicating that Buyang Huanwu Decoction could regulate lipid metabolism, reduce blood sugar, and correct metabolic disorders through multiple ways and targets.

4.2. Improve microcirculation of Nervous tissue

Wang Wenhui [20] et al. randomly divided the patients with diabetes peripheral neuropathy into a control group and a treatment group. The control group was given vitamin B1 and Intramuscular injection of methycobal. The treatment group was given Buyang Huanwu Decoction plus or minus formula on the basis of the control group. Both groups were observed for 30 days. The treatment results showed that the effective rate of the treatment group was far higher than the control group, with a significant difference, indicating that Buyang Huanwu Decoction could improve the microcirculation of Nervous tissue.

4.3. Promoting nerve regeneration and functional recovery

Xie Guoqing et al. [21] evaluated the protective effect of Buyang Huanwu Decoction on rat sciatic nerve injury model from aspects such as toe extension function (TSF), electrophysiology, and immunohistochemistry. The results showed that the TSF value of the Buyang Huanwu Decoction group reached its highest point 4 weeks after surgery, significantly better than the control group ($P<0.05$). The regenerated nerve structure was observed using transmission electron microscopy, and Schwann cell proliferation and myelinated nerve fibers were observed in the Buyang Huanwu Decoction group. The laminar structure was clear and the number increased, indicating that the Buyang Huanwu Decoction had a significant effect on promoting peripheral nerve regeneration.

4.4. Antioxidant stress

Guo Xiaohui et al. [22] compared and observed the cell proteins Lc3, Beckin1, and P62 in rat

model cells, and believed that Buyang Huanwu Decoction can not only promote cell autophagy, accelerate digestion, alleviate aging and disabled cells, provide raw materials for cell regeneration and reconstruction, but also inhibit excessive autophagy and reduce cell apoptosis by regulating the expression of Lc3, Beckin1, and P62 proteins, thereby achieving bidirectional regulation and protecting nerve cells. It is proved that Buyang Huanwu Decoction can effectively remove free radicals from injured Nervous tissue, improve microcirculation, reduce animal blood viscosity, and inhibit lipid peroxidation.

5. Clinical effect of Buyang Huanwu Decoction on diabetes peripheral neuropathy

Ningrui Table [23] selected 60 patients with DPN and randomly divided them into a treatment group and a control group with 30 cases each according to a random number table. On the basis of basic treatment, the control group was given 500ug/dose of mecobalamin tablets, taken orally three times a day, for 12 consecutive weeks; On the basis of the control group, the treatment group was supplemented with Buyang Huanwu Decoction (consisting of 50g Huangqi, 20g Raw Rehmannia, 20g Chuanxiong, 20g Red Peony, 15g Red Flower, 25g Peach Kernel, 20g Angelica Tail, 15g Dilong, 10g Leech, 15g Cinnamomum Cinnamomum Branch, and 3g Asarum) in 150ml per bag, one bag in the morning and one bag in the evening each day. Warm medication was taken after meals for 12 weeks. The treatment results showed that the improvement of TCM syndrome score in the treatment group was significantly lower than that in the control group. The improvement of limb numbness, limb pain, fatigue symptoms in the treatment group was better than that in the control group. The improvement of symptoms of shortness of breath, lazy speech, mental fatigue, spontaneous sweating and night sweating, and waist and knee tenderness in the treatment group was better than that in the control group. The TCM efficacy, MDNS score, and serum IGF-1 in the treatment group were better than those in the control group, indicating that Buyang Huanwu Decoction had obvious effects on diabetes peripheral neuropathy.

Xu Xia [24] selected 152 patients with DPN and divided them into two groups: the observation group and the control group, with 76 patients in each group. Both groups of patients received basic treatment for diabetes. 76 patients in the control group were treated with Lipoic acid injection on the basis of diabetes basic treatment, and 76 patients in the observation group were treated with modified Buyang Huanwu Decoction combined with Chinese herbal fumigation and washing on the basis of diabetes basic treatment. The results showed that the improvement of Hemorheology indicators in the observation group was significantly better than that in the control group, and the total effective rate in the observation group was significantly higher than that in the control group, suggesting that the modified Buyang Huanwu Decoction is effective in the treatment of diabetes peripheral neuropathy.

6. Summary

The onset of diabetes peripheral neuropathy is hidden, which is common in the late stage of diabetes. It is easy to cause limb ulceration or even amputation, which brings heavy burden to the life of patients. The traditional Chinese medicines such as Huangqi, Red Peony, and Angelica in Buyang Huanwu Decoction have the effect of antioxidant stress response, which can reduce neuronal damage through antioxidant stress response; The Active ingredient in Chuanxiong, safflower and other traditional Chinese medicines have multiple neuroprotective effects, which can effectively improve the function of peripheral nerve repair in patients; Traditional Chinese medicine such as peach kernel has anti-inflammatory and analgesic effects, which can alleviate patients' clinical symptoms. Therefore, we need to deeply explore the mechanism of Buyang Huanwu Decoction from the whole and different levels to provide basis for effective prevention and treatment of diabetes peripheral neuropathy, so as to promote the research of Buyang Huanwu Decoction on diabetes peripheral

neuropathy.

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