

Research Progress of Huanglian Wendan Decoction in Treating Diabetes Complicated with Insomnia

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Abstract: With the progress of the times and the fast-paced lifestyle, the key pathogenesis of diabetes has gradually changed. According to the clinical manifestations of modern diabetic patients, Gao et al. proposed the theory of damp-heat dissipation [3]. At the same time, according to clinical observation [4], patients with type 2 diabetes often accompanied by varying degrees of insomnia symptoms. Huanglian Wendan Decoction has now become a common prescription for the treatment of type 2 diabetes mellitus complicated with insomnia of damp-heat syndrome. This paper reviews the recent research progress of Huanglian Wendan Decoction in the treatment of diabetes mellitus complicated with insomnia by retrieving relevant literature in recent years, and provides a basis for further in-depth study and rational drug use.

Keywords: Type 2 diabetes, Huanglian Wendan decoction, Insomnia, Research progress

1. Introduction

Type 2 diabetes (T2DM) is a common metabolic disease characterized by hyperglycemia in clinic due to insufficient insulin secretion or insulin resistance, which is interacted by multiple factors. According to the latest IDF Diabetes Atlas, China has 140 million diabetics, ranking first in the world [1], mainly type 2 diabetes [2]. With the progress of the times and the fast-paced lifestyle, the clinical manifestations of patients with diabetes are mainly dampness-heat symptoms such as obesity, dry mouth, fatigue, abdominal distention, headache, dry stool or loose stool. The key pathogenesis of diabetes has gradually changed. Therefore, some doctors put forward the theory of “dampness-heat dissipation” [3]. At the same time, according to clinical observation [4], patients with type 2 diabetes often have varying degrees of insomnia. The probability of insomnia in patients with type 2 diabetes is higher than that in the normal population, and sleep disorder will further aggravate the disorder of glucose metabolism. Therefore, improving the sleep of patients with diabetes is conducive to the control of blood glucose. In clinical treatment, the therapeutic effect of Western medicine is not ideal, while the holistic view of traditional Chinese medicine, dialectical treatment, multi-target and multi-directional treatment of traditional Chinese medicine can achieve better therapeutic effect.

2. Analysis of etiology, pathogenesis and prescription

Type 2 diabetes with insomnia belongs to the category of “insomnia” in traditional Chinese medicine. Patients with type 2 diabetes are often affected by irregular diet, excessive appetite for fat and alcohol, and the evil of sweet and turbid is abundant in the body. Stagnation of phlegm in the body is easy to lead to phlegm heat, fire upside down, stop the heart orifices, disturb the mind and cause anxiety, yin and yang disorders and insomnia. Huanglian Wendan Decoction was derived from Qing·Lu Yanzhen’s “six-factor syndrome differentiation” and evolved from the “three-factor and one-disease-syndrome theory” of Wendan Decoction combined with Rhizoma Coptidis. The main drug components were Chenpi, Banxia, Fuling, Zhishi, Zhuru, Gancao, Rhizoma Coptidis, ginger and jujube. Huanglian Wendan Decoction is a reconciliation agent, which is mainly used for clearing heat and removing dampness, resolving phlegm and harmonizing stomach, relieving depression and removing annoyance. It is mainly used for the treatment of low fever, fullness and anorexia, nausea and vomiting, mouth distress, chest distress, insomnia and dreaminess, shallow sleep and easy to wake up, difficult to fall asleep after waking up, red tongue, yellow greasy moss, slippery pulse and other middle-jiao damp-heat diseases. Huanglian dry wet phlegm, heart purging fire; pinellia spleen and stomach, dry wet phlegm; zhuru clearing heat

phlegm trouble, and half summer with a cool ; chenpi combined with Fructus Aurantii Immaturus, combined with warming and cooling, increased the function of regulating qi and resolving phlegm ; poria spleen qi, to Du Shengtan source ; jujube invigorating spleen and stomach, regulating qi and tranquilizing mind ; the toxicity of ginger and stomach to Pinellia ; licorice reconciles drugs. The combination of various drugs is to clear heat and remove phlegm, yin and yang harmony, viscera qi and smooth, quiet and sleep.

3. Clinical Study on Huanglian Wendan Decoction in Treating Diabetes Complicated with Insomnia

3.1. Clinical Study on Huanglian Wendan Decoction in Treating Diabetes

Wang Mingkun, et al [5]. selected 60 patients with damp-heat accumulation type 2 diabetes and randomly divided them into observation group and control group. The control group was given metformin hydrochloride tablets, and the observation group was given Huanglian Wendan Decoction on this basis. Clinical studies have found that Huanglian Wendan Decoction combined with metformin hydrochloride can significantly reduce the TCM syndrome score of patients, significantly improve clinical symptoms such as thirsty and drinking, chest tightness and epigastric distention, head and body difficulties, fatigue, and stool discomfort, significantly reduce fasting plasma glucose (FPG), 2 h postprandial blood glucose (2 hPG), glycosylated hemoglobin (HbA1c), fasting insulin (FINS), triglyceride (TG), low density lipoprotein cholesterol (LDL-C) and free fatty acid (FFA) content, improve insulin resistance, with good clinical efficacy.Liu Li et al.[6] Sixty-eight patients with metabolic syndrome (MS) complicated with phlegm-heat syndrome of type 2 diabetes mellitus in the First Affiliated Hospital of Heilongjiang University of Traditional Chinese Medicine were selected. The control group was given routine treatment, and the observation group was treated with Jiawei Huanglian Wendan Decoction on this basis (basic prescription composition: Huanglian 10 g, Fuling 20 g, Banxia 15 g, Zhishi 10 g, Chenpi 15 g, Zhuru 10 g, Peilan 10 g, Gegen 15 g, Gancao 10 g. The changes of prescription and drug addition and subtraction: dry mouth plus raw gypsum 20 g, anemarrhenae 10 g, insomnia plus Fushen 30 g, Polygala 10 g, fatigue, shortness of breath plus astragalus 15 g, yam 15 g. After 8 weeks of treatment, it was found that the total effective rate of the observation group was 94.1 % , which was significantly higher than that of the control group, and the difference was statistically significant ($P=0.017$). Moreover, the levels of blood pressure, body mass index, TCM syndrome score, blood glucose index, blood lipid index, inflammatory factor and vascular endothelial function index in the two groups were significantly improved compared with those before treatment. The TCM syndrome score, fasting blood glucose, fasting insulin, steady-state model insulin resistance index, low density lipoprotein cholesterol, tumor necrosis factor α , leptin and endothelin 1 levels in the observation group were lower than those in the control group. The results showed that Huanglian Wendan Decoction combined with conventional methods in the treatment of MS patients with phlegm-heat syndrome of type 2 diabetes could reduce inflammatory response and improve vascular endothelial function, thereby controlling cardiovascular risk factors, and had high safety.Through the experimental study on SPF SD rats[7] , the rats were randomly divided into normal control group, model control group, metformin 0.25 g / kg group and Huanglian Wendan Decoction 3, 6 and 12 g / kg groups, with 10 rats in each group. After intragastric administration of the corresponding drugs or physiological saline, it was found that Huanglian Wendan Decoction could significantly reduce the contents of LPS, TNF- α and IL-6 in the serum of rats, and significantly increase the level of IL-10 in the serum. Significantly down-regulated Tlr4, Nf- κ b mRNA expression in colon tissue ; the protein expression of TLR4 and NF- κ B in pancreatic tissue was significantly decreased ($P < 0.05$ or $P < 0.01$), indicating that the mechanism of Huanglian Wendan Decoction in the treatment of type 2 diabetes mellitus is by regulating LPS / TLR4 / NF- κ B inflammatory signaling pathway, inhibiting inflammatory factors, thereby reducing blood glucose.Through network pharmacology[8], the results showed that the main effective components of Huanglian Wendan Decoction in the treatment of type 2 diabetes were quercetin, luteolin and other effective components, PTGS1, PTGS2, AR and other genes were the core targets of Huanglian Wendan Decoction in the treatment of type 2 diabetes. The targets of Huanglian Wendan Decoction in the intervention of type 2 diabetes were significantly enriched in the signaling pathways of late glycosylation end products – late glycosylation end products receptor, interleukin 17, tumor necrosis factor, etc. Studies have shown that the mechanism of Huanglian Wendan Decoction in the intervention of type 2 diabetes may be mediated by PTGS1, PTGS2, AR and other targets to regulate advanced glycation end products-advanced glycation end products receptor, interleukin-17, tumor necrosis factor signaling pathways to intervene in type 2 diabetes.

3.2. Clinical study of Huanglian Wendan Decoction on insomnia

Wei Jiaqi et al. [9] Selected 62 cases of insomnia patients with phlegm-heat disturbance type, and randomly divided them into control group and observation group, 31 cases in each group. The control group was given oral estazolam tablets before sleep, and the observation group was given Huanglian Wendan decoction. The study found that the total effective rate of the treatment group treated with Huanglian Wendan Decoction was as high as 96.8 %. The results showed that Huanglian Wendan Decoction significantly improved the clinical symptoms such as insomnia and dreaminess, chest wall stuffiness, bitterness and annoyance, dizziness and dizziness, significantly reduced the Pittsburgh sleep quality index (PSQI) score, and effectively improved the sleep quality of patients. Clinical research [10] was found that compared with the western medicine group of oral estazolam, the total effective rate of the traditional Chinese medicine treatment group with oral Huanglian Wendan decoction was 90.0 %, which significantly reduced the SDS, SAS score and PSQI scale, significantly improved the sleep quality, sleep efficiency and sleep disorders of patients, and had good clinical efficacy for the treatment of insomnia with phlegm heat disturbance. Ouyang Wenhui [11] selected 64 patients with insomnia due to phlegm-heat disturbance in Huichang County People ' s Hospital and randomly divided them into the control group and the observation group. The control group was treated with oral esazolam, and the observation group was treated with Huanglian Wendan Decoction on this basis. The results showed that the scores of chest tightness, insomnia, belching, bitter mouth, fatigue, dreaminess, head weight, yellow or yellow greasy tongue, slippery pulse or slippery number in the observation group were significantly lower than those in the control group, the clinical efficacy was better than that in the control group, and the Pittsburgh Sleep Quality Index (PSQI) score was lower than that in the control group, the differences were statistically significant ($P < 0.05$). It indicated that Huanglian Wendan Decoction combined with western medicine had good clinical efficacy in treating insomnia of phlegm-heat disturbance type, which could effectively relieve the clinical symptoms of patients, improve the sleep quality, and had high safety. Based on the theory of ' stomach disharmony is restless ', the network pharmacology study found [12] that Huanglian Wendan Decoction has the key selectivity of spleen, stomach and heart meridians. The main compounds were quercetin, tangerine, β -sitosterol, naringin, luteolin, etc. Mainly acting on interleukin-6 (IL-6), cyclin D1 (CCND1), vascular endothelial growth factor A (VEGFA), intercellular adhesion molecule-1 (ICAM1), fructooligosaccharides (FOS) and other core targets, as well as nuclear receptor activity pathway, neurotransmitter binding pathway, NF- κ B signaling pathway and other biological processes. The mechanism of Huanglian Wendan Decoction in treating insomnia may be the anti-inflammatory effect of flavonoids and inflammatory factors. Through clinical observation [13], it was found that Huanglian Wendan Decoction could up-regulate the levels of 5-HT, NE and GABA, and down-regulate the level of DA. At the same time, it also significantly improved the total sleep time, sleep latency, awakening time, sleep efficiency and other indicators of sleep EEG ($P < 0.05$ or $P < 0.01$). The results showed that Huanglian Wendan Decoction had obvious therapeutic effect on insomnia patients with phlegm-heat disturbance, and its mechanism might be related to its regulation of monoamine neurotransmitters.

3.3. Clinical Study on Huanglian Wendan Decoction in Treating Diabetes Complicated with Insomnia

Through clinical research [14], 60 patients with type 2 diabetes mellitus complicated with insomnia were randomly divided into the observation group and the control group. The observation group was treated with Huanglian Wendan Decoction, and the control group was treated with Estazolam. After six weeks of treatment, the results showed that Huanglian Wendan Decoction could significantly improve the sleep quality, sleep time, sleep efficiency, hypnotic drugs, daytime function score and FBG level of patients, and significantly reduce the Pittsburgh Sleep Quality Index (PSQI) score, which could effectively treat diabetes insomnia and help to control blood glucose. Lin Lin [15] Select diabetic patients with phlegm-heat disturbing heart insomnia, randomized controlled group and observation group, 50 cases in each group. The control group was treated with conventional hypoglycemic drugs or insulin to control blood glucose and diazepam tablets. The observation group was treated with hypoglycemic drugs or insulin to control blood glucose combined with Huanglian Wendan Decoction. The study found that the total effective rate of the observation group was 86.0 %, which was significantly higher than that of the control group. After treatment, the FBG levels of the two groups were lower than those before treatment, and the observation group was significantly lower than the control group, the differences were statistically significant ($P < 0.05$). Clinical studies have found [16] that compared with western medicine treatment with diazepam tablets before bedtime, Huanglian Wendan Decoction can significantly improve the sleep status, sleep time and sleep depth of patients, significantly reduce the fasting blood glucose level, and has small side effects. There is no rebound insomnia after drug withdrawal.

4. Conclusion

Insomnia is a common symptom in patients with type 2 diabetes, which is often recurrent and refractory. In view of the side effects and addiction of western medicine sleeping pills, patients' treatment compliance is poor, and Chinese medicine sleep aid is safe and effective, side effects are small, not easy to be addicted, and easy to be accepted by patients. Traditional Chinese medicine treatment of diabetes with insomnia still has broad prospects. In summary, Huanglian Wendan Decoction is effective in treating insomnia of obese type 2 diabetes and helps to reduce blood glucose, which is worthy of clinical application.

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