

# Progress in the Clinical Application of Huanglian Wendan Decoction in the Treatment of Cerebrovascular Disease

Ziliang Zhao<sup>1</sup>, Zhihong Yang<sup>2,\*</sup>

<sup>1</sup>Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China

<sup>2</sup>Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang 712000, Shaanxi, China

\*Correspondence Author

**Abstract:** *Huanglian Wendan decoction, as a widely used formula in clinical practice, is characterized by phlegm-fire originating from phlegm-fire, although the names and signs of the diseases it treats are different and the symptoms are complex. Therefore, for such diseases, Huanglian Wendan decoction can be used as the basis, with appropriate adjustments and additions, aiming at clearing heat and resolving phlegm, and strengthening the treatment strategy to enhance the clinical effect. Now, its clinical application in cerebrovascular diseases is summarized.*

**Keywords:** Huanglian Wendan decoction, Cerebrovascular disease, Clinical application.

## 1. Introduction

Huanglian Wendan decoction is derived from the modified Wendan decoction in the Song Dynasty's "Three Causes of Extreme Diseases and One Disease Square Theory" book, which is composed of Wen Gallbladder Soup plus Huang Lian and minus jujube. Huanglian Wendan decoction clears the gallbladder, harmonizes the stomach and removes phlegm, and is mainly used for treating bile-stomach disharmony and phlegm-heat internal disturbance of various syndromes. Zhang Jingyue recorded in the Class Classic that "although the liver is strong, it is not the gallbladder that keeps going, and when the liver and gallbladder follow each other, bravery is accomplished". It is written in the Nei Jing that "if the stomach is not in harmony, one will not be able to lie still". Gallbladder heat and wood depression, gallbladder loss of decision, resulting in timid and easily frightened, restlessness. When wood is depressed, liver qi is stagnant, qi is not smooth, phlegm qi is stagnant, resulting in the chest and epigastric region, then the chest is stuffy and disturbed, and phlegm and turbidity are covered in the upper part of the body, then dreams are abnormal. When phlegm and qi accumulate for a long time as phlegm-heat, phlegm-heat is disturbed internally and the gallbladder and stomach are not in harmony, then vomiting and retching will occur, and it will be difficult to sleep. Semixia is warm and hot in nature, good at removing phlegm and dampness in the stomach and stopping vomiting. Bamboo Root is cold in nature and is good at removing phlegm-heat, clearing phlegm-fire in the gallbladder and stomach and stopping vomiting. The combination of the two medicines, matching cold and heat, and the use of each other, play the role of clearing the gallbladder and stomach to resolve phlegm and stop vomiting. Tangerine peel is hard and warm in nature, which can strengthen the spleen and qi, dry dampness and remove phlegm. Tangerine peel is used with Pinellia to help Pinellia to smooth the qi of the spleen and stomach, so that phlegm and dampness will be removed when the qi is smooth. Poria is sweet and light in nature, strengthens the spleen and induces diuresis. Combined with Pinellia, it strengthens the spleen and dispels dampness, treats both symptoms and root cause, and solves the phlegm-dampness

generating origin in the middle jiao of the spleen and stomach. It strengthens the spleen and induces diuresis, dries dampness and resolves phlegm, and induces diuresis and tranquilizes the heart. Citrus aurantium is pungent and bitter, dispel Qi and eliminate stagnation. Tangerine peel rises more and lowers less, mainly rises, and Hovenia Citrus descends more and lowers less, mainly lowers. Citrus aurantium chenpi two medicines together, a rise and a fall, straight up and down, move qi and harmonize the middle, the gas line is wood, the qi smooth phlegm elimination. Ginger, jujube, licorice benefit the spleen and stomach and harmonize all medicines, playing the effect of clearing bile and stomach, regulating qi and resolving phlegm. If the bile heat is cleared, then the false annoyance and palpitation will stop, and if the stomach qi is harmonized, then the retching and sleeplessness will be cured. This formula is characterized by clearing the gallbladder and harmonizing the stomach to resolve phlegm. The key points of application are bitter mouth, greasy and yellowish coating, and slippery or numberless pulse. This recipe also has the function of clearing heat and resolving phlegm, which can be used to treat all cases of phlegm-qi stagnation and transforming into heat, and has wide clinical application. The clinical application of this formula to the cerebrovascular system in recent years is summarized as follows.

## 2. Stroke

Yang Hongsheng [1] selected 120 patients with stroke in the meridian (phlegm-heat congestion type), 60 cases of the control group were treated with aspirin enteric-coated tablets, atorvastatin calcium tablets, and hemosiderin injection medication, and 60 cases of the observation group were treated with Huanglian Wendan decoction, and the results showed that patients in the observation group's sleep quality, neurological function, motor function, and the ability to perform daily life had been significantly improved, and the effect was obvious. Yi Siqi [2] used Huanglian Wendan decoction on the basis of the control group for patients with cerebral infarction combined with diabetes mellitus, and the test showed that the test group had lower endothelial plaque area, endothelial intima-media thickness, and rate of

vulnerable plaques; lower levels of serum TC, TG, and LDL-C, and higher levels of HDL-C ( $P<0.05$ ), and higher levels of serum VEGF, and lower levels of sICAM-1 and IL-6 ( $P<0.05$ ), which could improve patients' sleep quality, neurological function, motor function, and ability of daily life. 0.05), which can improve the neurological function of patients with better safety. In Jiang Feiyuan's [3] study, on the basis of conventional anticoagulation treatment in internal medicine after neurointerventional thrombectomy for acute cerebral infarction, Huanglian Wendan decoction and Xinglou Chengqi decoction were added, and the scores of fainting, hemiparesis and aphasia of the treatment group were lower than those of the control group, the Barthel index was higher than those of the control group, and NIHSS score was lower than those of the control group, and the overall effective rate was higher than those of the control group, which proved that Huanglian Wendan decoction and Xinglou Chengqi decoction combined with neurointerventional thrombectomy for the treatment of acute cerebral infarction. This proves that Huanglian Wendan decoction combined with Xinglou Chengqi decoction combined with neurointerventional thrombectomy in the treatment of acute cerebral infarction can improve the degree of dizziness, hemiparesis, aphasia, and blood viscosity, reduce the neurological deficits, clinical efficacy and improve the quality of life. Through network pharmacological analysis, Dongxia Sun [4] suggested that Huanglian Wendan decoction may take  $\beta$ -sitosterol and soy sterol as the main core active ingredients, targeting key targets such as TNF and IL-1 $\beta$ , and regulating TNF and HIF-1 signaling pathways, suggesting that Huanglian Wendan decoction achieves its therapeutic effects on ischemic cerebral infarction through anti-inflammatory and anti-apoptotic effects. Stroke is a disease characterized by sudden fainting, unconsciousness, paralysis, distortion of the mouth and eyes, and unfavorable speech. Its pathologic causes include wind, fire, phlegm, qi and stasis. Excessive yang-heat dissipates fluid, and fluid is refined into phlegm, resulting in phlegm and fire, which causes phlegm and fire to rise, upward movement of clear orifices, internal movement of meridians and collaterals, resulting in stroke. Huanglian Wendan decoction is good at clearing away heat and resolving phlegm, and when phlegm and heat are eliminated, the stroke will be cured, and it is effective in treating phlegm fire disturbing the heart pattern type stroke.

### 3. Insomnia

Insomnia is characterized by difficulty in sleeping normally, and it is difficult to fall asleep and easy to wake up at night with intermittent sleep; or it is sleepless throughout the night. Chinese medicine and western medicine treatment of insomnia have their own characteristics. Western medicine is fast-acting but has dependence and side effects, while traditional Chinese medicine is green, economical and has little side effects, especially in the treatment of insomnia, which reflects unique advantages. Phlegm and heat disturb the mind and spirit as the main pathogenesis of insomnia, "The Complete Guide to Ancient and Modern Medicine" points out that "phlegm and fire disturb the mind and spirit, think too much, fire blaze and phlegm, which leads to insomnia." Adopting Huanglian Wendan decoction to solve the problem of insomnia by clearing away heat and resolving phlegm, regulating qi and harmonizing the stomach. Su Guochun [5]

added Huanglian Wendan decoction combination therapy on the basis of using eszopiclone to treat post-stroke insomnia, compared with the control group using eszopiclone and ghrelin tablets, the patients' sleep onset time, sleep duration, sleep quality, sleep efficiency, sleep disorders, and daytime function scores were significantly lower than those of the control group, and the CDR scores, HAMD, and HAMA scores were lower than those of the control group, and the MMSE scores were higher than those of the control group, improving the overall efficacy of post-stroke insomnia. Xing Lijie [6] used Huanglian Wendan decoction combined with Evodia Acupoint Application to compare with dexzopiclone for the treatment of post-stroke sleep disorders, and HAMA, HAMD scores, TCM syndrome scores and ADL scores were reduced compared with the pre-treatment period, and the degree of reduction in the Huanglian Wendan decoction was lower than that of the dexzopiclone group, and the levels of MBL scores, BDNF and 5-hydroxytryptophan were more significant and the level of elevated level of Huanglian Wendan decoction elevated the level of elevated level was more significantly, it suggests that Huanglian Wendan decoction combined with Evodia Acupoint Application for post-stroke sleep disorders can improve patients' TCM syndrome scores, improve sleep quality, alleviate the state of anxiety and depression, and the therapeutic effect is exact. Wu Shifu [7] treated post-stroke insomnia in patients with phlegm-heat internal disturbance type with modified Huanglian Wendan decoction and dexzopiclone. Through observation, the therapeutic effect of the observation group was better than that of the control group which used dexzopiclone alone, and the PSQI and HAMD scores, the Barthel Index, and the scores of insomnia, heartburn, chest tightness and epigastric congestion were all significantly improved in the observation group and lower than that of the control group. Feng Lei [8] used modified Huanglian Wendan decoction combined with acupuncture implantation to treat Cervical Insomnia caused by phlegm-heat Attacking Internally Type. Compared with the use of acupoint embedding treatment, the combination of modified Huanglian Wendan decoction resulted in a significant decrease in the patients' Pittsburgh Sleep Quality Index (PSQI) score, neck pain scale (NPQ) score, and TCM score, and significantly improved the patients' sleep disorders. Wu Jie [9] treated female menopausal insomnia patients with acupuncture implantation combined with modified Huanglian Wendan decoction. Compared with the control group of eszopiclone, in terms of improving the clinical efficacy and alleviating the discomfort of the patients, the TCM syndrome scores, the scores of the quality of sleep index (Pittsburgh Sleep Quality Index PSQI), as well as self-assessment scores of anxiety (SAS) and depression (SDS) were all decreased compared with their initial state after the treatment and all the indicators of the observation group were better than the control group, the monitoring of sexual hormone levels also confirmed the effectiveness of the treatment method. The effectiveness of the treatment was also confirmed by the monitoring of sexual hormone levels, which showed a decrease in FSH levels and a significant increase in E2 levels, especially when compared to the control group. The conclusion of this study points out that the use of acupuncture implantation combined with the addition and subtraction of Huanglian Wendan decoction in the treatment of female menopausal insomnia not only significantly improves the clinical symptoms, but also

effectively relieves the anxiety and depression of the patients and positively affects the sexual hormone levels in women, demonstrating the potential of this method in the treatment of this condition.

#### 4. Depression Syndrome

Depression syndrome is a disease caused by emotional disorders, characterized by depression, susceptibility to sadness and crying, and sleep disturbances. Anxiety and depression in Western medicine belongs to the category of this disease. The specific treatment of depression syndrome is to regulate qi, and in the process of treatment, we have to consider the situation of phlegm and qi inter-conjunction, phlegm-heat disturbing the spirit, and Huanglian Wendan decoction has the effect of clearing heat, regulating qi, and resolving phlegm. Liang Jianjun [10] in the use of Huanglian Wendan decoction combined with paroxetine for the treatment of post-stroke depression, compared with the use of paroxetine alone, the degree of reduction of SAS and SDS scores in the patient's combination group is more significant compared with the paroxetine group, which can improve the patient's psychological condition and quality of life, safe and effective. Wei Jinghua [11] in the use of Fluoxetine hydrochloride and stroke rehabilitation exercise for the treatment of post-stroke depression based on the joint use of Huanglian Wendan decoction, Huanglian Wendan decoction observation group HAMA, HAMD reduction are better than the control group, SF-36 score is higher than the control group, suggesting that the Huanglian Wendan decoction is effective in improving the post-stroke depression of the patient's state of anxiety and depression, increase the therapeutic efficacy, improve the quality of life of the patient. Chen Zhihui [12] took "phlegm fire" as the basic pathogenesis and used Huanglian Wendan decoction to treat patients with anxiety with taste loss, achieving good efficacy, and concluded that Huanglian Wendan decoction has sedative-hypnotic and anti-anxiety as its main effects. Yao Zhicong [13] conducted a group of prospective studies, through which it was found that Huanglian Wendan decoction, for patients with post-stroke depression and depressive disorders, can alleviate patients' anxiety and depressive state, improve patients' sleep quality, restore cognitive function, promote neurotransmitter regulation, and improve patients' daily life, and the clinical application of it is safe and efficient and worth to be popularized.

#### 5. Dementia

Dou Jinjin [14-16] demonstrated through experimental studies that the addition and subtraction of Huanglian Wendan decoction increased the activities of CAT, GSH-Px and SOD, decreased the activity of MDA, and significantly reduced the expression of TNF- $\alpha$ , COX-2, IL-1 $\beta$ mRNA, TNF- $\alpha$ mRNA and COX-2 mRNA in vascular dementia model rats, and inhibited inflammatory response through antioxidant, and played a therapeutic role in vascular dementia model rats. Therapeutic effects. Yang Qihan [17-18] added Huanglian Wendan decoction to the treatment of phlegm obstruction type Alzheimer's disease with oral donepezil, the therapeutic efficacy was significantly better than that of donepezil alone, and the levels of SOD, MMSE, MoCA, LMS, and QOL-AD scores were significantly higher, and the levels of TNF-alpha,

MDA, and ADAS-Cog, and the Behave-AD scores were significantly lower than those of donepezil alone. Bi Shuyue [19] also treated mild cognitive impairment with phlegm-heat internal disturbance evidence by combining Huanglian Wendan decoction with donepezil, and their MMSE, MoCA, and TCM evidence points were better than those of the donepezil alone group, improving the patients' mental status and cognitive function. Luo Leiling [20], on the basis of oral nimodipine treatment for post-stroke cognitive impairment, combined with Huanglian Wendan decoction combined with Yi'nao acupuncture, the patients' MoCA scores, and ADL scores improved more than those of the control group taking nimodipine alone. Similarly, Cao Yang [21] also used Huanglian Wendan decoction with acupuncture in combination with nimodipine, and the MSSS and MB scores were significantly improved, and the MMSE and ADL scores were significantly reduced compared with the nimodipine control group, both experiments suggest that Huanglian Wendan decoction in combination with acupuncture is used for the treatment of post-stroke mild cognitive dysfunction with significant clinical efficacy. Ma Guangxing [22] combined the use of Huanglian Wendan decoction combined with Zhisian acupuncture for the treatment of mild cognitive impairment in stroke, compared with the nimodipine control group, the study showed that the MoCA, MMSE, MBI scores with IGF-1, HDL of the Huanglian Wendan decoction treatment group were significantly higher than that of the control group, and the values of ADL scores, HCY, CRP, TC, TG, and LDL were significantly lower than that of the control group, which suggests that the combination of Huanglian Wendan decoction combined with Zhisian acupuncture has significant efficacy on cognitive impairment in stroke. This suggests that Huanglian Wendan decoction combined with Zhisian acupuncture has significant efficacy on cognitive impairment in stroke and improves the quality of life of VCI patients, and it also has the efficacy of lowering blood lipids, lowering homocysteine, and reducing the inflammatory response. Gong Yingbin [23] used Huanglian Wendan decoction to treat mild cognitive impairment in the elderly, compared with the control group, the total effective rate of the treatment group was significantly higher than that of the control group, and the adverse reactions were significantly lower than that of the control group, improving the cognitive function of the patients.

#### 6. Headaches

Headache is a common clinical symptom. When the function of the spleen and stomach is weakened, phlegm and dampness are not transformed, blocking the clear yang, and then upwardly violating the brain orifices, so that the clear yang does not rise and the turbid yin does not descend, resulting in headache, and the phlegm and turbidity cause stagnation of the qi and stagnation of qi and blood over a long period of time, which aggravates the headache with stagnation of blood and internal heat. Huanglian Wendan decoction can clear away heat and dissolve phlegm, and is effective in treating phlegm-heat headache. Yang Zhihong [16] used Huanglian Wendan decoction reductions treatment on the basis of dialectic patients for phlegm-heat headache, and achieved better efficacy. Chen Shaomei [17] believed that stubborn diseases are often accompanied by phlegm, phlegm becomes

heat over time, perturb the clear yang of heaven, blockage of qi generates phlegm-heat, resulting in headache attacks, the use of modified Huanglian Wendan decoction reductions subtractions for the treatment of new-onset daily persistent headache of phlegm-heat up to the blindfold, the patient's headache symptoms after three diagnoses of significant improvement. Wang Bao-liang [18] used Huanglian Wendan decoction to treat a migraine belonging to the liver and gallbladder heat, phlegm heat upturned, stasis of blood vessels obstructing the brain of the patient, in the Huanglian Wendan decoction on the basis of adding and then adding schizandra, dahuric dahuric root, rhizoma ligustici, Pueraria lobata, the whole scorpion, the stiff silkworms in order to pacify the liver and gallbladder heat, eliminate the heat of the gallbladder, dispel phlegm stasis, after taking for three weeks after the patient's headache symptoms disappeared, and then made into pills to take, the headache has not recurring. Zhao Yuefeng [27] used Huanglian Wendan decoction to treat patients with headache after microvascular decompression surgery with a combination of Chinese and Western medicine, and the study showed that the combination of Chinese and Western medicine was more effective than Western medicine alone.

## 7. Nephritis

Professor Fu Weimin [28] used Huanglian Wendan decoction to treat a patient with 4 years of vertigo caused by insufficient blood supply to the vertebral basilar artery, which was caused by internal deficiency of the liver and kidneys, and internal disturbance of phlegm and heat, and added white peony, calamus, Pueraria Mirifica, Tribulus terrestris, which worked together to pacify the wind and resolve phlegm, nourish the blood and collaterals, and achieved good therapeutic effect. Wen Xin [29] treated vertigo in hypertensive disease with Banxia Baizhu Tianma decoction combined with Huanglian Wendan decoction, and the improvement of the patients was significantly better than that of the conventional western medicine group. Cui Yanying [30] and An Mei [31] also did a similar study, and the results suggested that the combination of Banxia Baizhu Tianma decoction with Huanglian Wendan decoction had definite efficacy in the relief and control of vertigo. Wu Min [32] used Banxia Baizhu Tianma decoction combined with Huanglian Wendan decoction to treat hypertensive vertigo patients, after two weeks of treatment, the patients' SBP, DBP and PI were lower than those of the control group using only levamisole, and the VS and VD were all higher and higher than those of the control group, which could amicably improve the patient's hemodynamic indexes effectively. Li Hang [33] used Huanglian Wendan decoction combined with Banxia Baizhu Tianma decoction to treat hypertensive patients with vertigo, the patients' Hcy, hs-CRP and platelet aggregation were significantly better than that of the control group, which improved the patients' blood pressure, optimized the patients' Hcy, hs-CRP, and platelet aggregation, and reduced the incidence of adverse reactions in the patients. Wang Xi [34] used Huanglian Wendan decoction combined with acupuncture to treat phlegm-heat type vertigo in patients with Vs, Vd, and Vm values of the acupuncture group were higher than those of the traditional Chinese medicine group, suggesting that the combination of acupuncture and medicine can better improve the blood flow of the posterior cranial arteries and alleviate the effect of vertigo disorders. Cheng Wanren added Huanglian Wendan

decoction on top of duloxetine to treat patients with persistent postural perceptual dizziness with phlegm obstruction in the middle of the body, and compared with the control group using duloxetine alone, the level of decrease in DHI and HAMA of the patients was more significantly reduced compared with that of the control group.

## 8. Summary

To summarize, Huanglian Wendan decoction has been widely used in most cerebrovascular diseases with good therapeutic effects. In the face of cerebrovascular diseases caused by phlegm-heat syndrome, it is necessary to carry out a detailed dialectic treatment of the patient's physique, symptoms, and pathogenesis, and to appropriately adjust the combination of medicines or supplement it with acupuncture, in order to enhance the efficacy of the treatment, and at the same time, the integration of the results of modern pharmacology is aimed at expanding the application of Huanglian Wendan decoction in the treatment of phlegm-heat syndrome of various types of cerebrovascular diseases. At the same time, the integration of modern pharmacological results aims to broaden the application prospects of Huanglian Wendan decoction in the treatment of various types of cerebrovascular diseases belonging to the phlegm-heat syndrome.

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