

Research Progress of Traditional Chinese Medicine in Treating Gastroesophageal Reflux Disease of Liver-stomach Disharmony Type

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Abstract: *Gastroesophageal reflux disease (GERD) is one of the most common chronic gastrointestinal disorders. Although its incidence varies according to geographical regions, the prevalence of GERD has increased in recent years, and there is a tendency for the population to become younger. Chinese medicine focuses on the holistic concept and evidence-based treatment, which can regulate the patient's symptoms from the physiological and psychological aspects as a whole, and has good therapeutic effects. This article introduces the research progress of the treatment of liver-stomach disharmony syndrome of GERD from four aspects: traditional Chinese medicine internal treatment, acupuncture treatment, combined traditional Chinese and Western medicine, and other treatments.*

Keywords: Gastroesophageal reflux disease, Liver-stomach disharmony syndrome, Traditional Chinese medicine.

1. Introduction

Gastroesophageal reflux disease (GERD) is a common digestive disorder characterized by acid reflux and heartburn, often accompanied by nausea, belching, and retrosternal pain. Studies have shown that there are geographical differences in the incidence of GERD, with the incidence in North America ranging from 18.1%-27.8%, East Asia from 2.5%-7.8% [1], and the prevalence of GERD in China is about 7.69%, with a tendency to rejuvenation [2]. Smoking, obesity, alcohol consumption, and overfeeding are risk factors for the development of GERD [3], and the age of the diseased population is mostly concentrated in the age of 50 years or older, often accompanied by chronic gastritis and other chronic underlying diseases [4]. Not only does it have a negative impact on the quality of daily life of patients, but it also creates a certain economic burden. Therefore, it is crucial to emphasize the prevention and treatment of GERD. Western medicine treatment of GERD mainly focuses on the protection of gastric mucosa and acid suppression, which has the advantage of quick effect, but is prone to adverse reactions and has poor long-term effect after stopping the drug [5]. Traditional Chinese medicine (TCM) treats GERD mostly from the liver and stomach theory, and it has definite efficacy. This article aims to summarize the research progress of TCM treatment of liver-stomach disharmony type GERD.

2. TCM Causes and Mechanisms

In traditional Chinese medicine, GERD is classified as one of several conditions, including "acid reflux," "acid swallowing," "plum-pit qi," "stomach rumpus," and others. The disease is located in the esophagus and stomach, closely related to the liver and spleen, and the basic mechanism is that the stomach is out of harmony and the turbid qi is upwardly reversed [6]. Jingyue Quanshu [7] states that the spleen and stomach qi deficiency and middle-aged gradually weakened, and the diet is reduced, sometimes resulting in the occurrence of acid reflux and vomiting. The Collected Supplement to Syndrome Identifications and Treatments adds that vomiting acid is a result of irritation, anger, and depression can all

contribute to injury to the liver and gallbladder qi. Wood can produce fire, which can invade the spleen and stomach. This can result in the inability to digest food, which can then accumulate in the stomach and cause acidity. This process is known as "immersion of the disease." Dietary disorders, emotional disorders, and vegetative weakness can all contribute to the development of this disease. Huo Jiaxin [8] based on the study of 392 cases of GERD patients, summed up a total of nine types of syndromes, including liver and stomach disharmony syndrome, liver depression and spleen deficiency syndrome, liver and stomach depression and heat syndrome, of which the liver and stomach disharmony syndrome accounted for 43.36% of the total syndrome type. The Theory of Blood Syndrome [9] posits that: Dietary qi into the stomach, all rely on the liver qi to its excretion, so that the food is digested. The liver is responsible for excretion, can regulate the whole-body qi, coordination of the spleen and stomach elevation, the spleen and stomach for the human body qi of the pivot. If the liver fails to regulate, liver qi stagnation, invading the spleen and stomach, stomach qi retrogrades upward, liver and stomach disharmony, then it is easy to appear emotional depression, nausea, belching and acid swallowing and other symptoms, which in turn formed the liver and stomach disharmony type GERD.

3. Therapeutic Methods

3.1 Internal Treatment with Traditional Chinese Medicine

In Chinese medicine, according to different geographical areas, people's physique and other factors, the formulas for treating liver-stomach disharmony type GERD are different, but the overall principle of treatment is to dredge the liver and harmonize the stomach. These formulas can regulate intestinal flora and gastrointestinal hormone levels, improve anxiety and depression, which can not only significantly relieve symptoms in the short term, but also reduce the recurrence rate in the long term, so that patients can get a better therapeutic effect.

Zhang Nan et al. [11] randomly divided 80 cases of refractory gastroesophageal reflux disease (RGERD) patients with liver and stomach disharmony syndrome into an experimental group and a control group, with 40 cases in each group. The experimental group was given the Shugan Hewei Formula (Bupleuri Radix, Cyperi Rhizoma, Fructus Aurantii, the stem of Inula Flower, Hematite, Rhizoma Coptidis, Medicinal Evodia fruit, Gardenia Jasminoide, Calcined ark shell, Siberian Solomonseal rhizome, Fritillaria thunbergia, Medicinal Magnolia Bark, Ginger), and the control group was given the formula of Esomeprazole Magnesium enteric-coated tablets combined with Mosapride Citrate dispersible tablets orally, with the treatment course of both groups being 8 weeks. The comparison of the Chinese medicine symptom score and Gastroesophageal Reflux Disease Questionnaire (GERD-Q) score of the two groups of patients showed that the efficacy rate of the experimental group (82.5%) was significantly higher than that of the control group (65%), and the Alpha diversity analysis showed that the Chao1, Ace, sobs, and Shannon indices of the experimental group were increased to a higher level than that of the control group ($P < 0.05$). While the taxonomic composition analysis of bacterial species showed no significant difference between the two groups at the phylum level, the relative abundance of Subdoligranulum, norank_f_Oscillospiraceae, and Monoglobus increased, and the relative abundance of Ruminococcus_gnavus_group decreased at the genus level, which indicated that the Shugan Hewei Formula might effectively improve the clinical symptoms of patients by increasing the diversity of the intestinal bacterial flora and regulating the abundance of some bacterial genera.

Tang Liming et al. [11] treated patients with RGERD with Xuanfu Daizhe Decoction, and the results showed that the total effective rate of the treatment group was 90% after 4 weeks, which was significantly higher than that of the control group (62.5%), and the patients showed improvement in the Pittsburgh Sleep Quality Index (PSQI), Hamilton Anxiety Scale (HAMA) scores, Hamilton Depression Scale (HAMD) scores, and clinical symptom scores compared with the pre-treatment period. In addition, after 4 weeks of treatment, the levels of plasma gastrin (GAS) and motilin (MTL) were significantly higher in both the treatment and control groups. It is worth noting that only patients treated with Xuanfu Daizhe Decoction had significantly lower plasma levels of cholecystokinin (CCK) and vasoactive intestinal peptide (VIP), which are gastrointestinal hormones that can reduce lower esophageal sphincter pressure, suggesting that Xuanfu Daizhe Decoction not only improves clinical symptoms and sleep quality, alleviates patients' anxiety and depression, but also regulates gastrointestinal hormone levels and promotes the recovery of lower esophageal sphincter function.

He Meijun et al. [12] treated non-erosive gastroesophageal reflux disease (NERD) liver-stomach disharmony syndrome with the Shugan Jiangni Hewei Formula (Bupleuri Radix, Rhizoma Pinelliae, Liquorice root, Chuanxiong, Chenpi, Fructus Aurantii, Cyperi Rhizoma, Radix Paeoniae Alba, Hematite and Inula Flower) for 8 weeks of treatment compared with the Western medicine group (omeprazole), and the results showed that patients in the herbal medicine group had significantly fewer gastrointestinal symptoms, lower scores on anxiety and depression, and were able to more

significantly reduce serum nerve growth factor (NGF) and substance P (SP) levels, suggesting that its mechanism of action may be related to the reduction of visceral hypersensitivity.

Wang Jie et al. [13] administered the self-designed Chaishao Tongjiang Formula to the traditional Chinese medicine treatment group and rabeprazole sodium enteric-coated tablets orally to the control group, and found that after 8 weeks of treatment, the Chaishao Tongjiang Formula was able to significantly reduce the Reflux Disease Questionnaire (RDQ) scores and Gerd-Q scores, increase the overall efficacy of treatment, improve the patients' quality of life, and improve the state of anxiety and depression. After 1 month of treatment, the relapse rate of the treatment group (15.2%) was significantly lower than that of the control group (41.7%). This indicates that Chaishao Tongjiang Formula is superior to the single use of Western medicine in improving symptoms, improving quality of life and preventing relapse, and is worth popularizing and applying.

Li Tong et al. [14] treated liver-stomach disharmony type NERD using Modified Liver-inhibiting Powder (Bupleuri Radix, Angelica Sinensis, Chuanxiong, stir fried Atractylodes Macrocephaly, Poria Cocos, Gouteng and Hypericum Perforatum), which had a higher overall efficacy rate than that of the Western oral drug rabeprazole enteric capsules, and significantly reduced symptom scores, self-rating anxiety scale scores, self-rating depression scale scores, and the incidence of adverse reactions.

Zhao Zeshi [15] observed 44 cases of liver-stomach disharmony pattern in GERD and gave the patients Sini San and Sijunzi Decoction plus Reduction with a control comparison before and after the treatment of the patients, and the results show that the total TCM symptom points, major symptom points, and minor symptom points of the patients were significantly reduced after the treatment. This indicates that Sini San combined with Sijunzi Decoction can not only effectively alleviate the main symptoms such as heartburn, epigastric distention and reflux, but also have a significant effect on the secondary symptoms such as abdominal pain, belching, constipation, sticky stool and emotional discomfort.

3.2 Acupuncture Treatment

Acupuncture treatment for GERD liver-stomach disharmony syndrome usually selects the liver meridian of foot-Jueyin, the stomach meridian of foot-Yangming acupuncture points such as Qimen, Taichong, Zusanli, Hegu, etc., and also selects the spleen meridian of foot-Taiyin Acupuncture points such as Gongsun, Sanyinjiao and the corresponding Back-Shu points. Acupuncture can affect the autonomic nervous system, regulate gastrointestinal hormone secretion, improve digestive tract dynamics, and reduce inflammatory reactions [16]. It takes acupuncture points based on the theory of the five elements of Chinese medicine, replenishing the deficiency and diarrhea, which can regulate the organism in both directions and achieve the purpose of harmoniously conditioning the Five Zang organs and regulating the Qi movement.

Wang Xuejiao et al. [17] found that by observing 138 patients,

on the basis of domperidone capsules, the five meridians were used to regulate qi, and the acupoints of Qimen, Neiguan, Zhongwan, Tianshu, Taichong, Zhusanli, and Xingjian were selected for needling, and the serum Ghrelin and VIP, as well as TNF-alpha and IL-8 of the patients, were significantly improved after 14 days of treatment ($P < 0.05$). It indicates that five meridians compatibility to regulate qi acupuncture can adjust human body functions, reduce clinical symptoms, and improve the inflammatory response situation.

Zou Yi [18] randomly divided 82 patients with refractory reflux esophagitis into two groups, on the basis of conventional Western medicine treatment (rabeprazole capsule), the observation group received acupuncture (Zhongwan, Zusanli, Weishu, Neiguan, Taichong, Hegu, Gongsun), and the control group was given placebo acupuncture (non-meridian, non-acupuncture superficial needling), and the results showed that the improvement of the RDQ scores and the Chinese medicine syndrome scores of the observation group were superior to those of the control group after 8 weeks ($P < 0.05$), and both HAMA scores and HAMD scores improved and had a superior effect than the control group after treatment ($P < 0.05$). At the later follow-up, the anxiety and depression scores of the patients in the observation group showed a more pronounced tendency to decrease during weeks 8-20 compared to the control group. And the relapse rate of the observation group (12.8%) was lower than that of the control group (29.7%), indicating that acupuncture treatment could not only alleviate uncomfortable symptoms and improve the anxiety and depression, but also reduce the relapse rate, which had a significant advantage in the long-term efficacy.

Zhang Lili et al. [19] investigated the effects of liver-stomach disharmony type reflux esophagitis (RE) on serum GAS and MTL, and the Western medicine plus Chinese medicine plus acupuncture group was treated with acupuncture based on oral omeprazole enteric-coated capsule and Banxia Xiexin Decoction, and selected the main acupoints of Xinshu, Weishu, Pishu, Dushu, Tanzhong, Zhongwan, Zusanli, and Sanyinjiao. The results showed that the combination of TCM harmonization method and acupuncture treatment could significantly increase the serum GAS and MTL levels, improve the gastrointestinal function, reduce the recurrence rate, and improve the quality of life of the patients.

3.3 Combination of Chinese and Western Medicine

Han Dongwen [20] selected 80 patients to observe the efficacy of the Self-designed Tiaoshen Hewei Decoction in the treatment of liver-stomach disharmony-type RGERD. The control group was given a double dose of omeprazole enteric-coated capsules, and the treatment group was given orally with the combination of the Self-designed Tiaoshen Hewei Decoction on top of the regular dose of omeprazole. After 8 weeks of treatment, the overall efficacy rate of the treatment group (89.74%) was higher than that of the control group (60.52%) in terms of Chinese medicine symptom scores, and the treatment group had a more pronounced alleviating effect on the patients' psychosomatic state in terms of self-rating anxiety scale scores and self-rating depression scale scores. In terms of the total score of the RDQ scale, the clinical symptoms of the treatment group were more

obviously reduced, indicating that the self-designed Tiaoshen Hewei Decoction could effectively reduce the clinical symptoms of the patients, especially in improving mood and sleep quality, which was more effective than the single Western medicine treatment.

Luo An [21] on the basis of oral rabeprazole enteric-coated capsules in the control group, the treatment group was given the addition of Sini San combined with Chaihu Jia Longgu Muli Decoction, and the results showed that the treatment group had a more obvious efficacy in alleviating the clinical symptoms such as acid reflux and retrosternal pain. The results of TCM symptom scores and HAMA and HAMD total scores also indicated that the treatment group was not only effective in reducing the primary symptoms of TCM, but also performed well in improving the secondary symptoms of TCM, such as appetite, chest tightness, good sighing, nausea and desire to vomit, as well as combating negative emotions. The results of the 1-month follow-up at the end of the treatment showed that the relapse rate of the treatment group was significantly lower than that of the control group (13.33% vs. 40.00%), which also showed its advantage in long-term efficacy.

Ma Lingling [22] used Biling Weitong Granules combined with rabeprazole in the treatment of NERD with liver and stomach disharmony syndrome, and found that its total efficacy rate of 93.33% was higher than that of the control group, and it could better inhibit gastric acid, which not only effectively alleviated the symptoms of gastrointestinal tract, but also regulated the mental and psychological state of patients from the whole, and improved the quality of life.

Zhang Lan [23] was given rabeprazole sodium combined with Mosapride in the control group, and the test group was added Tongjiang Shuge Soup. After 4 weeks of treatment, patients in the test group had lower GERD-Q scores. After 2 weeks and 4 weeks of drug discontinuation, the recurrence rate in the test group was 5.00% (2/40) and 7.50% (3/40), respectively, which was statistically significant ($P < 0.05$) compared with 17.50% (7/40) and 22.50% (9/40) in the control group. It indicates that Tongjiang Shuge Soup combined with Western medicines can effectively improve patients' clinical symptoms and reduce the risk of recurrence.

Gao Huixia [24] studied the effect of Shugan Hewei Decoction combined with rabeprazole in the treatment of liver-stomach disharmony-type RE, and the results showed that the total effective rate of the Shugan Hewei Decoction group was significantly higher than that of the Western medicine group, and it was able to reduce the frequency and duration of gastric reflux, increase the number of lactic acid bacteria and bifidobacteria in the intestinal tract, and reduce the number of enterococcus and enterobacteria, and the clinical efficacy was safe and stable.

Shi Zhenguo et al. [25] selected 80 patients with liver-stomach disharmony syndrome RE as the study subjects, and they found that the addition of Banxia Xiexin Decoction combined with Western medicine treatment could obviously improve the patients' Chinese medicine symptom scores, to improve the levels of serum GAS and MTL, and alleviate the symptoms of ergotism belching and depression, giving full

play to the strengths of the combination of traditional Chinese and Western medicine treatments.

3.4 Other Treatments

In addition to conventional acupuncture and oral drug therapy, catgut embedding therapy and acupoint application are also effective for this disease. Huang Jianchun and others [26] randomly divided 70 patients with GERD of the liver-stomach disharmony type into two groups. The treatment group was given acupuncture point submerged treatment by the Shengyang Yiwei acupoint thread embedding therapy (the main points of the first course were selected as Tiantu, Danzhong, Zhongwan, and double Geshu; the main points of the second course were added to the double Zusanli; and the main points of the third course were then added to the double Gongsun), while the control group was given omeprazole enteric capsules orally, and the treatment course for both groups was 12 weeks. The results of the study showed that acupoint therapy could significantly increase the lower esophageal sphincter pressure, upper esophageal sphincter pressure, distal esophageal contraction integra, reduce the time of esophageal acid exposure and the number of acid reflux, and improve the quality-of-life scores, showing a good therapeutic effect on GERD. Zhang Ying [27] on the basis of oral omeprazole magnesium enteric-coated tablets and Mosapride citrate tablets in the control group, the observation group was given the addition of traditional Chinese medicine acupoint application therapy, and the acupoints were Pishu, Weishu, Geshu, Sanjiaoshu, Ganshu, Danshu, and Zhongwan, and the medicines consisted of Medicinal Evodia fruit, Clove, Rhizoma Pinelliae, Aurantii Fructus Immaturus and Medicinal Magnolia Bark. The results showed that the Gerd-Q score and the Short-Form Renux-Qual score of the observation group were better than that of the control group after treatment ($P < 0.01$), and the efficacy of gastroscopic inflammation of the observation group was better than that of the control group ($P < 0.05$), which indicated that the combination of acupoint application therapy with conventional acid-inhibiting and pro-gastrointestinal drugs could improve the quality of life of patients, and it was an effective treatment in the clinic.

4. Discussion

GERD is a prevalent chronic gastrointestinal disorder. The pathogenesis of liver-stomach disharmony in this disease is based on the stagnation of liver qi and upward reversal of stomach qi. The treatment should be based on the principle of soothing the liver and regulating qi, and harmonizing the stomach to lower rebelliousness. The efficacy of traditional Chinese medicine in the treatment of liver-stomach disharmony type GERD is exact, which can clearly improve the symptoms, regulate the systemic state, reduce the adverse reactions, and the therapeutic effect is stable and safe. Especially, it is outstanding in relieving anxiety and depression, and it can reduce the recurrence of the subsequent disease, which can make up for the insufficiency of easy recurrence after stopping the drug after the treatment of pure Western medicine, and it is worth to be popularized and applied in the clinic. The mechanism may be related to reducing visceral hypersensitivity, improving esophageal dynamics, regulating gastrointestinal hormone secretion, and

promoting gastric emptying. Whether it is Chinese medicine treatment or Western medicine treatment, internal treatment or external treatment, combination therapy is better than monotherapy, which is an indication of the importance of combining Chinese and Western medicine to fully utilize their respective advantages and complement each other's strengths and weaknesses. Anxiety and depression are very common in patients with GERD of Liver-stomach Disharmony type, which is easy to form a vicious cycle of " anxiety - exacerbation of illness - anxiety ". Therefore, in clinical treatment, in addition to differentiating and treating syndromes and alleviating the clinical symptoms of patients, we should also pay attention to the mental and psychological health of patients, and help patients to build up their confidence, so as to improve the quality of life of patients.

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