Study on the Mechanism of Sishen Wan's Anti-Irritable Bowel Syndrome

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Abstract: Irritable bowel syndrome (IBS) refers to a group of clinical syndromes that include abdominal pain, bloating, changes in bowel habits, changes in stool characteristics, and mucous stools. It is persistent or recurrent, and can be caused by examination. These symptoms are organic diseases. This disease is the most common type of functional intestinal disease. The patients are mostly young and middle-aged, and the first onset is rare after the age of 50. The course of the disease is protracted and repeated, and the symptoms have long been troubled by patients, affecting the quality of life, and causing great psychological and economic burdens. At present, there is no special treatment for this disease. The author uses the classic traditional Chinese medicine Sishen Pill to treat patients with diarrhea-type irritable bowel syndrome, and has achieved good clinical results. The report is as follows. Objective: To observe the clinical effect of modified Sishen Pills in the treatment of diarrhea-type irritable bowel syndrome. Method: Sixty patients with diarrhea-type irritable bowel syndrome (spleen and kidney yang deficiency syndrome in TCM) were randomly divided into treatment group and control group. The treatment group was treated with Sishen Pills, and the control group was treated with Bifidobacterium Sanlian Live Bacteria Capsules. Use compound diphenoxylate tablets together, and observe the effect after 2 weeks of treatment. Results: Comparison of the scores of abdominal pain and diarrhea before and after treatment between the treatment group and the control group, the difference was statistically and significant ($P < 0.05$); the treatment group and the control group had no statistically significant difference in the curative effect of abdominal pain and diarrhea ($P > 0.05$); The treatment group and the control group have a statistically significant difference in the efficacy of TCM syndromes ($P < 0.05$). Conclusion: Modified Sishen Pills can treat diarrhea-type irritable bowel syndrome (spleen-kidney yang deficiency syndrome in TCM). It has good curative effect in improving abdominal pain and diarrhea symptoms and TCM syndromes, and has no obvious adverse reactions.

1. Introduction

Irritable bowel syndrome is an intestinal disorder that excludes organic causes and has chronic and recurrent bowel frequency changes, abnormal stool characteristics, and abdominal pain or abdominal discomfort. It is one of the most common clinical functional gastrointestinal diseases. First, it has the characteristics of high morbidity and high recurrence rate, which seriously affects people's quality of life. According to the clinical symptoms of patients, IBS can be divided into constipation type (IBS-C), diarrhea type (IBS-D), mixed type (IBS-M) and uncertain type (IBS-U). Clinically, diarrhea-type irritable bowel syndrome (IBS-D) is the most common, accounting for about 75% of the prevalence. In recent years, with changes in diet, lifestyle and psychological stress, the incidence of IBS has increased year by year. There are reports in the literature that the global prevalence of IBS is 11.2%. Western countries have a relatively high prevalence rate of 4.7% to 25%, while the prevalence of IBS in Asia and Africa is relatively low, ranging from 6.5% to 10.1%. IBS not only has a high population prevalence rate, but also persists and is difficult to heal. The symptoms exist for a long time, which seriously affects the quality of life of patients, and at the same time occupies a large amount of medical resources. Therefore, more and more researchers have paid more and more attention to it, and they have conducted more extensive and in-depth research.

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2. Materials and Methods

IBS-D TCM diagnostic criteria and TCM spleen-kidney-yang deficiency criteria are formulated in accordance with the “Guiding Principles for Clinical Research of New Chinese Medicines”: The number of stools increased, more than 3 times a day, accompanied by changes in stool volume and traits (daily stool volume exceeded 300 g or more is irregular loose stools) or frequent watery stools within a certain period of time; diarrhea with a course of more than 2 months or recurrent diarrhea intermittently within 2 to 4 weeks. TCM syndrome differentiation criteria for spleen and kidney yang deficiency: Main symptoms: ① Loose stools and diarrhea; or clear and thin stools (may be accompanied by non-removal of grains); spondylolisthesis; or diarrhea after five changes; ② abdominal pain; ③cold-shaped limbs. Secondary symptoms: ① limb fatigue; ② reduced diet; ③ soreness of waist and knees; ④ mental fatigue and laziness. Tongue and pulse: ①The tongue is pale and fat, and the fur is white and moist; ②The pulse is heavy and thin or weak. “Consensus Opinions on Diagnosis and Treatment of Irritable Bowel Syndrome” of the Chinese Medical Association Gastroenterology Branch: Symptoms have been at least 6 months before diagnosis, and recurrent abdominal pain or discomfort symptoms have occurred at least 3 days a month in the last 3 months, combined with the following 2 Strips or more: ①Symptoms relieved after defecation; ② Changes in the frequency of bowel movements during the onset: bowel movements> 3 times a day; ③Changes in the stool characteristics (appearance) during the onset: loose stools (mushy stools) or watery stools ⩾25%.

The pathogenesis of IBS is not yet clear. Stress, abnormal gastrointestinal motility, intestinal infection, visceral hypersensitivity, brain-gut axis dysfunction, and mental stress are considered to be important related factors. In the 1990s, Weston et al. believed that the onset of IBS may be related to low-grade intestinal inflammation and low-grade immune activation in the intestine. More and more evidences show that IBS-D is an immune-inflammatory mode of gastrointestinal disease. In recent years, domestic and foreign scholars' research on the pathogenesis of IBS is still the intestinal mucosal low-grade inflammation and immune factors. Studies have shown that there are abnormalities in multiple links of the 5-HT signaling system when IBS-D occurs, which is manifested by increased 5-HT levels in plasma, hypothalamus and colon, decreased MAO-A enzyme activity, and decreased expression of SERT and 5-HT4R. The expression level of 5-HT3R is elevated. Research by Liu Xiubo and others found that the expression levels of IL-6 and IL-23 in the intestinal mucosa of the terminal ileum and ascending colon of IBS patients were significantly higher than those of healthy people. IL-6 and IL-23 may be important pathogenic factors of IBS and may be related to IBS. The clinical symptoms are related. When analyzing the serum inflammatory cytokines of patients with diarrhea-type irritable bowel syndrome, He Xiaorong and others found that serum TH1 pro-inflammatory cells TNF-α, IL-12, IFN- γ, and IL-8 in IBS patients increased, and TH2 anti-inflammatory Compared with the control group, the levels of IL-4 and IL-10 in cells showed no significant difference.

3. Preliminary Study on the Quality Determination of Experimental Drugs

①Meet the diagnostic criteria of Western medicine diseases; ②Meet the diagnostic criteria of TCM syndromes; ③Age ⩾18 years old, ⩽75 years old, gender is not limited; ④Persons who voluntarily accept the trial treatment of this drug and sign an informed consent. Exclusion criteria ①Complications caused by surgical operation within 30 days before the test; ②Use of drugs for the treatment of IBS within 1 week; ③Use of antibiotics within 7 days; ④Pregnant or lactating women; ⑤People with allergies, drug or food allergies History or allergies to the known components of the test drug; ⑥Combined with severe primary diseases such as cardiovascular, lung, liver (AST, ALT> 2 times normal), kidney (Cr> upper limit of normal), brain and hematopoietic system, etc., malignant Patients with tumors, mental illnesses, hyperthyroidism, and diabetes; ⑦Stools routinely have abnormalities such as white blood cells, pus cells, phagocytes, or infectious diarrhea that

cannot be ruled out; ⑧Stool occult blood test is positive, and other organic intestinal properties cannot be ruled out People with illness; ⑨Participants in other drug clinical trials 3 months before the test; ⑩One of the following alarm symptoms: Symptoms are severe at night or affect sleep; with fever, anemia, blood in the stool or black stool, significant weight loss, and Symptoms of bowel obstruction; abdominal mass. General data collection From June 2011 to May 2012, there were a total of 60 outpatient and inpatient cases in this hospital, all of which met the diagnostic criteria of western medicine and the dialectical classification criteria of traditional Chinese medicine. Number the patients according to the order of admission, check the random number table with random numbers, and divide them into two groups according to the principle of randomization, which are respectively recorded as the treatment group and the control group. There was no significant difference in the general condition of the two groups of patients after statistical treatment ($P>0.05$), and they were comparable.

Treatment group: Sishen pills plus flavor, medicinal: nutmeg 10 g, psoralen 10 g, schisandra 10 g, evodia 6 g, red ginseng 10 g, Bupleurum 10 g, white peony 10 g, Citrus aurantium 10 g, Roasted licorice 6 g. This prescription is made into vacuum packaging by the Chinese pharmacy of our hospital using a decoction machine. Each package is 125 mL, 1 package each time, and is taken twice in the morning and evening. No other western medicine is used during the treatment. Control group: Bifidobacterium triple viable capsules (Peifeikang) daily, 3 times/d, combined with compound diphenoxylate tablets 2 capsules for severe diarrhea, 3 times/d, after the diarrhea is controlled, Reduced use). The treatment course of the two groups was 2 weeks. 1.6 Observation indicators 1.6.1 Safety indicators Blood routine: Record once before and after treatment 2 times in total). Routine examination of urine and feces: before treatment and once after treatment 2 times in total). Liver function (ALT, AST, TBIL), renal function (BUN, Cr) examination: each test before and after treatment (2 times in total). ECG examination: 1 test before and after treatment 2times in total). Observation of possible adverse drug reactions: record at any time. IBS curative effect judgment index: abdominal pain, diarrhea (feces and stool characteristics). Indicators for the efficacy of TCM syndromes Main symptoms: abdominal pain, diarrhea, cold limbs; Secondary symptoms: fatigue of the limbs, reduced diet, weakness in the waist and knees, and lazy speech; (3) Tongue and pulse: The tongue is pale and fat, the coating is white and moist; the pulse is heavy and thin or weak. Efficacy evaluation criteria Safety evaluation Laboratory tests include: routine blood, urine and stool routine tests, liver function (ALT, AST, TBIL), renal function (BUN, Cr) tests, and electrocardiogram. During the experiment, pay close attention to the adverse events, adverse reactions, and serious adverse events of the subjects. Judgment of the curative effect of IBS The clinical curative effect of diarrhea is evaluated according to three levels: markedly effective, effective and ineffective. Efficacy criteria for diarrhea: Significantly effective: the sum of defecation frequency and trait scores is reduced by $\geqslant$70% compared with before medication; Effective: the sum of defecation frequency and trait scores is reduced by $\geqslant$30%, but <70%, compared with before medication; invalid: defecation The sum of frequency and trait scores decreased by <30% compared with that before medication. Criteria for determining the efficacy of abdominal pain: markedly effective: the patient's classification is reduced by 2 levels or more after treatment; effective: the patient's classification is reduced by one level after treatment; ineffective: the patient's classification is still at the same level or higher than the original level after treatment. Criteria for the efficacy of TCM syndromes Clinical recovery: The symptoms and signs disappear or basically disappear, the syndrome score is reduced by $\geqslant$95%; markedly effective: the symptoms and signs are significantly improved, and the syndrome score is reduced by $\geqslant$70%; effective: symptoms, all signs have improved, and the syndrome score is reduced by $\geqslant$30%; Ineffective: Symptoms and signs are not significantly improved, or even worsened, and the syndrome score is reduced by <30%. Note: The calculation method (Nimodipine method) is: (Integral before treatment-integral after treatment) ÷ integral before treatment] × 100%. Statistical analysis the statistical analysis of the data was performed using IBM SPSS 20.0 software. All statistical tests adopt two-sided tests, and the test level is $\alpha = 0.05$. Measurement data are expressed as mean ±

standard deviation (x x ± s), using t test; rank data using rank sum test.

4. Experimental Results

In this experiment, the wavelength of 245 nm was selected to quantify the two components of psoralen and isopsoralen. The chromatograms of the mixed reference substance and the sample are shown in Figure 2. The results showed that the retention times of the peaks of psoralen and isopsoralen in the test solution were 22.036 min and 29.786 min, respectively, and the number of theoretical plates was greater than 6000.

The intraday and interday RSD of psoralen were 0.85% and 1.40%, respectively. The intra-day and inter-day RSD of isopsoralen were 0.63% and 1.17%, respectively. The same extract was injected and analyzed at 5 time points, and the RSD of psoralen was 1.26% and the RSD of isopsoralen was 1.39%, indicating that the methanol extract of Sishen pill was stable within 48 hours. The peak areas of the test products psoralen and isopsoralen are 15359782 and 12917536, respectively. Taking the control quality concentration as the abscissa (X) and the corresponding peak area as the ordinate (Y), draw a standard curve. The linear equation of psoralen and the correlation coefficient (r) are Y=192.65 X+39609 (r=0.9997), The linear equation and correlation coefficient (r) of isopsoralen are Y = 207.63 X + 33645 (r = 0.9996). It is calculated that the content of psoralen per lg of this product is 0.6903%, and the amount of isopsoralen is calculated as 0.3410%, and the result meets the pharmacopoeia standards. Psoralen and isopsoralen in the test solution are isomers, and chromatographic separation is the main way to determine the isomers. In this experiment, the drugs were identified by referring to the identification method of Sishen pill in the 2015 edition of the Pharmacopoeia, and a thin-layer chromatography identification method for psoralen and isopsoralen in Sishen pill was established. The method is simple to operate and can be used for the thin layer of Sishen pill. Identification to improve the quality of Sishen pill. The main clinical form of traditional Chinese medicine is compound prescription. This experiment follows the traditional preparation method originally recorded in Sishen pill prescription, and prepares the decoction by decoction as the test solution for the study. The extraction method is more in line with the real situation of the actual clinical guidance of Chinese medicine in the patient's medication.

5. Discussion and Conclusion

IBS is a chronic functional bowel disease characterized by abdominal pain, bloating, and changes in bowel habits. In traditional Chinese medicine, it belongs to the categories of “diarrhea” and “abdominal pain”, which also has a certain relationship with “stagnation syndrome”. Modern medicine believes that changes in gastrointestinal dynamics, visceral hypersensitivity, brain-gut axis regulation dysfunction, and autonomic nervous and hormonal disorders are the most important pathophysiological basis of IBS. Genetics, environment, intestinal infections, and social psychology are An important pathogenic factor of IBS. At present, western medicine treatment is mainly psychological intervention treatment, dietary treatment and symptomatic treatment of drugs, but this can only have a certain effect on some patients and the symptoms are easy to recur after treatment. Although the patient’s diarrhea and abdominal pain stopped temporarily, the patient still had many conscious symptoms that could not be completely eliminated, such as cold limbs, fatigue, depression, sighs, etc. Clinicians are very troublesome with these symptoms, and combined with western medicine for antidepressant The treatment effect is not satisfactory. Based on the above reasons, the author explored the treatment of irritable bowel syndrome with traditional Chinese medicine. According to Wang Ang's view that “chronic diarrhea is caused by kidney life and fire failure, and cannot be dedicated to the spleen and stomach.” Acute syndrome, spleen and kidney yang deficiency. In the prescription, psoralen is bitter and heat-replenishing, and it is an essential medicine for strengthening fire and soil; nutmeg warms the spleen and kidneys and astringent intestines to relieve diarrhea; Warming and invigorating the yang of the spleen and kidney, combined with Sini Powder to harmonize the liver and spleen, the whole prescription can not only warm the spleen and kidney, but also soothe the liver and regulate the spleen. The gratifying clinical

effect obtained in this clinical research not only reflects the improvement or elimination of the main symptoms of abdominal pain and diarrhea, but also the patient's conscious symptoms have also been significantly reduced or eliminated. This clinical effect is significantly better than the current pure western medicine group. For this reason, the author believes that Chinese medicine may have a great future in the treatment of irritable bowel syndrome. Due to the limitations of the research conditions, there are still many issues that need further research in this study, such as how does the addition of Sishen Pill affect gastrointestinal motility, how to regulate neuroendocrine and visceral hypersensitivity, and whether the prolonged course of treatment is positive for the effect. Whether related and integrated traditional Chinese and Western medicine is more effective and economical in the treatment of irritable bowel syndrome, it is hoped that it will be further improved in future research.

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