

## Therapeutic Analysis of Fuzi Lizhong Wan with Trimebutine in the Treatment of Diarrhea Type Irritable Bowel Syndrome

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**Funding:** Youth Scientific Research Fund project of Affiliated Hospital of Hebei University (2016Q003).

**Abstract: Objective:** To evaluate the clinical efficacy of Fuzi Lizhong Wan and trimebutine in the treatment of diarrhea irritable bowel syndrome. **Methods:** A total of 90 patients with diarrhea irritable bowel syndrome were divided into control group ( $n=45$ ) and treatment group ( $n=45$ ) using the random number table method. Patients in the control group were administered with trimebutine 0.2 g, three times daily for 4 weeks. Patients in the treatment group were administered with Fuzi Lizhong Wan 9 g, three times daily for 4 weeks on the basis of the control group. The clinical efficacy and the TCM symptom scores were evaluated after treatment. The serological indicators in two groups were compared before and after treatment. **Results:** After treatment, the clinical efficacy and the TCM symptom scores in treatment group were significantly lower than that in control group ( $P<0.05$ ). The levels of serological indicators in both groups improved significantly, and those in the treatment group were better than the control group ( $P<0.05$ ). **Conclusion:** Combined therapy of Fuzi Lizhong Wan and trimebutine in the treatment of diarrhea type irritable bowel syndrome has a significant effect, which can relieve clinical symptom, and reduce visceral sensitivity, and improve levels of inflammatory and quality of life. So it is suggested to be applied.

**Key words:** Fuzi Lizhong Wan; Trimebutine; Diarrhea irritable bowel syndrome

**Publication date:** July, 2020

**Publication online:** 31 July, 2020

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Irritable bowel syndrome (IBS) is a functional bowel disease, with abdominal pain, bloating or discomfort as the main symptoms. The symptoms are relieved after defecation, often accompanied by changes of defecation habits [frequency and (or) traits]. The report of organic lesions that can be found by routine clinical examination is not available to explain these symptoms<sup>[1]</sup>. The incidence of IBS has been reported to be 5.8%-17.5%, of which women have a higher prevalence<sup>[2,3]</sup>. The disease is divided into 4 types, including constipation, diarrhea, mixed and indefinite type, of which diarrhea type is the most common. The clinical manifestations of this type of patients are abnormal fecal traits (diluted stool or watery stool) and abnormal frequency of stool (The frequency of bowel movements >3 times/day) and recurring abdominal pain are the main ones, which seriously damage the physical and mental health of patients<sup>[4]</sup>. IBS seriously affects the quality of life of patients and costs a lot of medical expenses<sup>[5,6]</sup>. Therefore, the treatment of IBS is particularly important and urgent. The goal of treatment is to alleviate the symptoms of abdominal pain and improve the condition of stool, and ultimately to improve the quality of life of patients. At present, the choice of drugs for Western medicine is mainly trimebutine maleate, but some patients have poor treatment results. Diarrhea-type of irritable bowel syndrome belongs to the category of "diarrhea" and "abdominal pain" in traditional Chinese medicine. It is mostly caused by

the deficiency of the spleen and kidney yang which leads to the dysfunction of spleen and stomach. Fuzi Lizhong Wan is Chinese patent medicine which can warm up and strengthen the spleen and stomach. It can be applied to the symptoms as abdominal cold and pain, vomiting and diarrhea. Therefore, this research aimed to explore the therapeutic effect of Fuzi Lizhong Wan combined with trimebutine maleate in the treatment of diarrhea irritable bowel syndrome.

## 1 Materials and Methods

### 1.1 Normal information

90 patients with diarrhea irritable bowel syndrome admitted to the Affiliated Hospital of Hebei University from July 2016 to May 2018 were selected, including 41 males and 48 females; aged 21-58 years, with an average age of  $(35.71 \pm 3.28)$  years old; the course of disease is 6 months to 10 years, with an average course of  $(4.1 \pm 1.2)$  years. There was no significant difference between the two groups in terms of gender, age and course of disease and other general data ( $P > 0.05$ ), which was comparable. This study has been approved by the hospital ethics committee, and all patients voluntarily signed informed consent.

### 1.2 Standard of selection

(1) All selected cases have undergone clinical and laboratory examinations, excluding gastrointestinal organic, cardiac and respiratory system, endocrine and metabolic system, connective tissue diseases and important organ diseases. There is no history of abdominal surgery<sup>[7]</sup>; (2) It complies with IBS Rome IV diagnostic criteria<sup>[8]</sup>; (3) And it is in accordance with spleen and stomach type of yang deficiency in Diagnosis and Treatment Guidelines for Common Diseases of Internal Medicine of Traditional Chinese Medicine-TCM Disease Section<sup>[9]</sup>; (4) All patients did not take gastrointestinal motility drugs, laxatives, antidiarrheal drugs, microecologics, antidepressants or other drugs 2 weeks ago.

### 1.3 Drugs

The control group intake trimebutine maleate capsules (Shanxi Zhendong Ante Biopharmaceutical Co., Ltd.; approval number: State Food and Drug Administration H20040713; specifications:  $0.1 \text{ g} \times 12 \text{ capsules} \times 2 \text{ plates}$ ). The applied dose is 0.2 g each time, 3 times a day for 4 weeks. The

observation group are added Fuzi Lizhong Wan on the basis of the control group (Beijing Tong Ren Tang Technology Development Co., Ltd. Pharmaceutical Factory; approval number: State Food and Drug Administration Z11020053; specification:  $9 \text{ g} \times 10$  pills). The applied dose is 9g each time, 3 times a day for 4 weeks of treatment.

### 1.4 Method

Indicators of observation and judgment of efficacy Comparison of the symptom scores between the two groups of patients; comparison of the TCM symptom scores between the two groups of patients before and after treatment; comparison of the serum 5-HT, IL-1 $\beta$ , IL-10 and NPY levels between the two groups of patients before and after treatment.

#### 1.4.1 Clinical symptom score

Defecation frequency (times/d): 0 points (<3 times)<sup>[10,11]</sup>

2 points (3-4 times)

4 points (5-6 times)

6 points ( $\geq 7$  times)

Stool traits: 0 points (like snake or sausage, with smooth surface)

2 points (soft and lumpy, with smooth edges)

4 points (mushy stool with thick and fluffy edges)

6 points (no solid lump, and it is water-like)

#### 1.4.2 TCM symptom scores refer to Diagnosis and Treatment Guidelines for Digestive Diseases in Traditional Chinese Medicine

Symptoms and signs (mainly including abdominal pain, bloating, diarrhea, incomplete bowel movements and tongue veins) are divided into: Negative: asymptomatic<sup>[12]</sup>; Mild: mild symptoms, or occasional seizures; Moderate: more obvious symptoms, or frequent attacks; Severe: The symptoms are very obvious and even unbearable. Syndrome points were recorded before and after treatment, and syndrome points =  $[(\text{pre-treatment points} - \text{post-treatment points}) / \text{pre-treatment points}] \times 100\%$ .

#### 1.4.3 Detection of serological index is conducted before and after treatment by drawing 5 ml of fasting venous blood from the two groups of patients in the morning

After centrifugation, the upper layer of serum was taken and stored at  $-80 \text{ }^\circ\text{C}$ , using ELISA kit to conduct detection (Shanghai Enzyme Biotechnology Co., Ltd.).

## 1.5 Statistical analysis

The statistical software SPSS 23.0 was used to process the data. The count data was expressed as percentage and the  $\chi^2$  was used to test; the dose data was expressed as  $\bar{x} \pm s$  and the t test was selected.

## 2 Results

### 2.1 Comparison of symptom scores between two

**Table 1.** Comparison of symptom scores between two groups of patients

Group	n/case	time	Scores of stool frequency	Scores of stool trait
Control group	45	before	4.57±1.19	4.61±1.35
		after	1.10±0.53*	1.33±0.35*
Observer group	45	before	4.86±1.25	4.72±1.28
		after	0.79±0.21* <sup>▲</sup>	0.71±0.14* <sup>▲</sup>

Compared with the pre-treatment in the same group: \* $P<0.05$ ; compared with post-treatment in the control group: <sup>▲</sup> $P<0.05$

### 2.2 Before treatment, there was no statistically significant difference in TCM (Traditional Chinese Medicine) symptom scores between the 2 groups ( $P>0.05$ )

After treatment, a comparison of pre-treatment was made in the control group and the observer group

**Table 2.** The two groups were compared before and after treatment

Group	Cases	Pre-treatment	Post-treatment	Score difference
Control group	45	9.90±0.35	2.05±1.83*	7.75±0.69
Observer group	45	12.95±1.68	1.47±0.55*	12.33±0.57 <sup>▲</sup>

Compared with pre-treatment in the observer group, \* $P<0.05$ ; compared with post-treatment in the control group, <sup>▲</sup> $P<0.05$ .

## 3 Discussion

IBS is one of the most common gastrointestinal functional diseases, and its onset may be related to various factors such as intestinal motility disorders, visceral hypersensitivity, infection inflammation, psychology, stress and genetics. At present, the incidence of IBS is getting higher and higher. Although this disease is a functional bowel disease, its pathogenesis is diversified, and the symptoms recur repeatedly. It is so serious that it affects the patient's life and work. After spending a lot of money for medicine and occupying medical resources, it often can not get satisfactory treatment results. Therefore, it is crucial to clarify its pathogenesis and find effective drugs for therapy. Studies have shown that the occurrence of IBS is closely related to gastrointestinal infections, and it is found that the levels of inflammation-related factors in IBS patients

## groups of patients

After treatment, the stool frequency and trait scores of the two groups were significantly lower than pre-treatment; the difference between pre-treatment and post-treatment in the same group was statistically significant ( $P<0.05$ ); after treatment, the symptom score of the observation group was significantly lower than that of the control group. The difference is statistically significant ( $P<0.05$ ).

respectively. The TCM symptom score decreased, and the difference was statistically significant ( $P<0.05$ ). A comparison of the TCM symptom score difference between pre-treatment and post-treatment was made, and the observer group was significantly better than the control group ( $P<0.05$ ).

are increased. If they can be effectively treated, the levels of inflammatory factors will be reduced. IL-1 $\beta$  is an inflammatory cytokine, which is widely involved in various pathological damage processes such as tissue destruction and edema formation. It accelerates the occurrence of inflammatory reactions, and can increase visceral sensitivity, trigger intestinal dysfunction, and accelerate the development of IBS. IL-10 is an anti-inflammatory cytokine, which can inhibit the release of inflammatory mediators from mononuclear macrophages. In addition, it can enhance the release of anti-inflammatory cytokine. If its level increases, it suggests the recovery of inflammation. 5-HT is an important neurotransmitter involved in regulating the movement and secretion function of the gastrointestinal tract. About 95% of the 5-HT in the human body comes from the digestive tract, mainly the enterochromaffin cells (EC) of the mucosa, which contains tryptophane hydroxylase needed for compounding 5-HT. Affected

by pressure and chemical stimulation in the intestinal cavity, EC cells will secrete 5-HT. 5-HT acts on the 5-HT receptors on the neuron of afferent nerve under mucous membrane. It stimulates peristaltic reflexes, and regulates intestinal secretory function. 5-HT can increase the visceral sensitivity and the contraction of gastrointestinal tract movement, and promote diarrhea. NPY is widely distributed in the central and peripheral nervous systems. It promotes the release of pain-causing neurotransmitters, and plays a role in antagonizing stress, stabilizing emotions and sedation. It has a significant inhibitory effect especially on L cell secretion of ileum and colon and gastrointestinal motility and secretion<sup>[13]</sup>.

At present, in the clinical treatment of IBS, trimebutine maleate is mostly used. It is a gastrointestinal motility regulator. This medicine directly applies on calcium and potassium ion pathways on the smooth muscle cell membrane of the gastrointestinal tract. It can prevent internal flow of calcium ions or external flow of potassium ions. It can also achieve the regulation of excitement and inhibition, and played a two-way regulation on gastrointestinal motility<sup>[14]</sup>. It can improve clinical symptoms such as abdominal pain and diarrhea.

Diarrhea-type IBS belongs to the category of "abdominal pain" and "diarrhea" in traditional Chinese medicine. Studies have shown that the efficacy of traditional Chinese medicine intervention is significant<sup>[15]</sup>. TCM believes that normal spleen and stomach luck depends on the function of kidney yang warming, so kidney yang deficiency and spleen and stomach dysfunction affect spleen and stomach luck and cause diarrhea. Therefore the disease caused by spleen and kidney yang deficiency should be considered<sup>[16]</sup>. For treatment, we use Fuzi Lizhong Wan for warming the spleen, dispelling cold, and stopping diarrhea and pain. This medicine consists of aconite (processed), Codonopsis, Atractylodes (fried), dried ginger and licorice. Among them, the aconite (processed) has the effects of promoting the yang and invigorating the internal heat, and warming up spleen and kidney. The modern pharmacological study of aconite has anti-inflammatory and analgesic effects. Codonopsis has the effect of anchoring minds, tonifying spleen, invigorating qi and encouraging production of body fluid. According to modern pharmacological studies, Codonopsis has antagonism against 5-HT, histamine, so as to

regulate the movement of the gastrointestinal tract; Atractylodes macrocephala (fried) has the effects of eliminating dampness, increasing secretion of urine, and invigorating spleen and qi. Modern pharmacological research shows that it can regulate gastrointestinal movement. Dried ginger also has the effects of warming, removing cold and diarrhea. Modern pharmacological research shows that it has the functions of promoting digestion and stopping diarrhea; licorice has the effect of invigorating spleen and qi. The combination of various medicines can achieve the effects of relieving cold, invigorating qi and spleen, and preventing diarrhea and pain.

In this study, traditional Chinese medicine and western medicine were combined for diarrhea-type IBS treatment. Not only it takes effect from traditional Chinese medicine curing congenital base of life and warming both spleen and kidney, but also uses western medicine to adjust the intestinal function. The combination of Chinese and Western medicine can relieve abdominal pain and diarrhea. The research results show that it can significantly relieve patients' symptoms, improve brain-gut function and inflammatory cytokine levels, improve patients' quality of life, and has certain value for clinical application.

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