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CLINICAL EXPERIENCE

Effect of Tongxie Yaofang (痛泻要方) Granule in Treating Diarrhea-Predominate Irritable Bowel Syndrome*

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ABSTRACT **Objective:** To study the clinical effect of Tongxie Yaofang (痛泻要方, TXYF) Granule in treating diarrhea-predominate irritable bowel syndrome (D-IBS) and its possible mechanism. **Methods:** A total of 120 patients were assigned to two groups using stratified block randomization, 80 in the intervention group and 40 in the control group. To the intervention group the TXYF granule was given at one package each time, twice a day; the control group was treated with Miyarisan three times a day, two tablets each time. The course of treatment was 4 weeks for both groups. The total efficacy in them was compared, and data of scoring on stool (Bristol method), abdominal pain, abdominal distension, and mental condition were collected before treatment and 2 and 4 weeks after treatment. The activation of mast cells (MCs) of six patients chosen from each group was detected as well before and after treatment. **Results:** No significant difference between the two groups in terms of the total efficacy or the scores of symptoms before and after treatment was found ($P>0.05$). The number of activated MCs was decreased in the intervention group after treatment, showing significant difference as compared with that before treatment as well as with that in the control group after treatment ($P<0.01$). **Conclusions:** TXYF is an effective preparation for the treatment of D-IBS. It can quickly lessen abdominal pain and distention, improve the property of stool, and improve mental tension and depression in patients. Its mechanism of action might be through the adjustment of MCs activation to decrease visceral hypersensitivity.

KEY WORDS Tongxie Yaofang Granule, diarrhea-predominate irritable bowel syndrome, clinical observation

Irritable bowel syndrome (IBS) is a syndrome characterized by abdominal pain and/or discomfort, accompanied by changes in defecation habits. Special effective measures for IBS have been lacking till now due to its unclear pathogenesis. An epidemiologic investigation carried out in the United States showed that the morbidity of IBS is 15% to 22%, with 5 million patients consulting doctors every year due to IBS, and medical expenses reaching up to 80 hundred million US dollars[(1)]. Investigations by scholars in China have shown that the morbidity of IBS in Guangzhou residents is 5.6%, with 10.1% of patients having to visit general internal medical clinics for IBS and 34.3% having to visit special clinics of digestive diseases[(2)].

Bio-benefiting enterobacterial preparation is the drug frequently used for the treatment of IBS in current clinical practice. However, it is unsatisfactory as it takes time to be effective, yet is liable to cause drug-resistance and is expensive as long-term medication. For these reasons people are seeking new and more economical and effective measures from Chinese herbal preparation. Good efficacy was gained by the authors in treating diarrhea-predominate irritable bowel syndrome (D-IBS) by using the traditional Chinese medicine (TCM) preparation Tongxie Yaofang (痛泻要方, TXYF) Granule, and the study is reported herein.

METHODS

Diagnostic Standard

In reference to the Rome Ⅲ standard[(3)], patients could be diagnosed as D-IBS once when they have symptoms of recurrent abdominal pain or discomfort that have lasted more than 6 months, at least for three days each month, and are accompanied by two or more items of the following conditions in the latest three months: (1) the symptoms can be

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alleviated after defecation; (2) changes in the daily frequency of defecation; (3) changes in the property and appearance of stools during attacks. Moreover, electronic enteroscope examinations should be done to exclude organic diseases.

General Materials

Using the sample estimation program of the statistical software STATA 5.0, setting α=0.05, β=0.1, bilateral test, inter-group ratio 2:1, the authors had the size of samples preconcerted as 120 cases in total, 80 in one group and 40 in the other group. All the 120 patients were inpatients or outpatients of the authors' hospital from March 2006 to June 2008, and were assigned to two groups using stratified block randomization. The 80 patients in the intervention group consisted of 33 males and 47 females, 39.2 $\pm$13.4 years old, with an illness course of 6.3$\pm$4.6 years; the 40 in the control group consisted of 17 males and 23 females, 37.5$\pm$15.6 years old, with an illness course of 5.9$\pm$4.5 years. No significant difference between them was shown by statistical analysis (*P*>0.05).

Treatment

Miyarisam (a product of Miyarisam Co., Japan, batch number: 174061) was orally administered to patients in the control group, two tablets each time, three times a day; patients in the intervention group were treated with TXYF granule, a Chinese herbal preparation produced by Jiangyin Tianjiang Pharmaceutical Co., Ltd. (Jiangsu Province, China), every package containing extract from white atractylodes rhizome 15 g, saposhnikovia root 8 g, tangerine peel 6 g, and white peony root 12 g. It was orally taken one package each time, twice a day. The therapeutic course for both groups was 4 weeks. The treatment could be discontinued in good time when patients felt it was intolerable or when they were unwilling to continue the treatment.

Scoring on the Overall Symptoms of IBS

Scoring on the overall symptoms of IBS in the following four aspects was performed: Bristol scoring on the stool, abdominal pain and distension, and mental condition was performed before treatment (T0) and at the end of the 2nd and the 4th week of treatment (T1 and T2) in the weekly revisit.

The criteria for property of stool scoring were established in reference to Bristol scoring[4] as follows: sausage-like or snake shape stool, slippery and soft, was scored as 0; soft mass with clear confines as 2; fluffy with unclear confines or mushy stool as 4; and watery stool with no solid component as 6. The criteria for abdominal pain scoring were defined in reference to literature[5] as follows: mild degree, coming occasionally each day and that can be relieved spontaneously, was scored as 2; moderate degree, often occurring but tolerable, as 4; severe degree, obvious pain always occurring every day, mostly intolerable, as 6. The criteria for scoring abdominal distension[5] were: mild degree, occasional attacks that can be automatically alleviated in about half an hour was scored as 2; moderate degree, always existing attacks that cannot be alleviated in 1-2 h, as 4; severe degree, unrelieved distension all day long with medication needed, as 6. The criteria for scoring mental disordering[5] were: mild degree, slight discomfort that does not affect sleep was scored as 2; moderate degree, anxiety, depression, that affects sleep, but can be adjusted by oneself, as 4; severe degree, worrying, excitement, even delirium, that has a bad impact on sleep and cannot be adjusted by oneself, as 6.

Detection of Mast Cell Activation

The detection on the activation of mast cells (MCs) was performed in six cases of each group before and after treatment. Three pieces of colonic membrane biopsy were taken by Olympus 230 enteroscope. The samples were fixed by 10% neutral formalin, and examined with refined toluidine blue stain[6] by a pathological physician. The positive cells, e.g. the activated MC in three randomly selected high-power visual fields ($\times$400), were counted and their mean value was used in statistical analysis.

Standard for Therapeutic Efficacy

The efficacy of treatment was evaluated depending on the efficacy index (EI), which was calculated by the Nimodipine method with the formula: EI (%) = (pre-treatment TSS – post-treatment TSS)/ pre-treatment TSS $\times$ 100%, where TSS in the formula means the total scores of symptoms. The efficacy was defined as cured when the patient's symptoms disappeared with the EI equal to or over 95%; as markedly effective when patient's symptoms were obviously alleviated with EI equal to or over 70% but less than 95%; as effective when the patient's

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symptoms were alleviated with EI equal to or over 30%, but less than 70%; and as ineffective when no or only slight change of symptoms was found with EI lower than 30%.

Statistical Analysis

One-way analysis of variance (ANOVA) was used for the data of normal distribution, and *Ridit* test to analyze the rank sum data between two groups. The statistical software applied was SPSS 11.5 for Windows. $P<0.05$ was regarded as having statistical significance.

RESULTS

Of the 80 cases in the intervention group, 3 dropped out in the follow-up, which were not analyzed or explained due to the less than 20% drop-out rate; the follow-up study was completed in all 40 patients in the control group.

Comparison of Total Efficacy between Groups

Ridit analysis showed that the total efficacy on clinical symptoms between groups was not significantly different ($P>0.05$, Table 1), the total effective rate was 90.9% (70/77) and 92.5% (37/40) in the intervention group and the control group, respectively.

Table 1. Comparison of Total Efficacy between Groups (Case)

Group	Case	Cured	Markedly	Effective	Ineffective
Intervention	77	64	3	3	7
Control	40	34	2	1	3

Comparison of Symptom Scores between Groups

The scores symptom scores, including all items like property of stool, abdominal pain and distension, and mental condition, were reduced significantly after treatment in both groups, showing significant difference as compared with those before treatment ($P<0.01$), but showing insignificant difference between groups ($P>0.05$, Table 2). The results suggested that both TXYF and Miyarisam have the same and definite effect in improving the symptoms of D-IBS.

Comparison of MCs Activation between Groups

Microscopic examination showed that MCs were distributed around the small vessels at mucosal and sub-mucosal layers, round or spindle-shaped or irregular shaped, with purple stained plasma and blue nuclei. The degranulated MCs showed intact cytomembrane and broken cytomembrane with granules effusing out, whereas the in-degranulated MCs showed integral cytomembrane and homogeneous plasma, and the nucleus was surrounded by granules in scattered shape (Figure 1). The number of activated MC in the intervention group decreased significantly after treatment, showing significant difference to that before treatment ($P<0.01$), whereas it was unchanged in the control group ($P>0.05$). Thus, the difference between groups after treatment was also significant ($P<0.01$, Table 3).

DISCUSSION

Depending on clinical manifestation, traditional Chinese medicine classifies IBS into the categories of diarrhea or abdominal pain. Its pathogenesis is the discord of the Pi (脾) and Gan (肝). In the components

Table 2. Comparison of Symptom Scores between Groups (Score, $\bar{x} \pm s$)

Group	Case	Time	Property of stool	Abdominal pain	Abdominal distension	Mental condition	Total score
Intervention	77	T0	5.39 ± 0.26	5.82 ± 0.18	5.46 ± 0.34	5.50 ± 0.32	22.17 ± 0.22
	77	T1	3.25 ± 0.27*	3.47 ± 0.21*	3.28 ± 0.22*	3.34 ± 0.27*	13.34 ± 0.21*
	77	T2	2.46 ± 0.28*	2.82 ± 0.38*	2.65 ± 0.29*	2.13 ± 0.24*	10.06 ± 0.23*
Control	40	T0	5.42 ± 0.16	5.70 ± 0.30	5.51 ± 0.24	5.70 ± 0.22	22.23 ± 0.19
	40	T1	3.29 ± 0.21*	3.43 ± 0.17*	3.23 ± 0.15*	3.35 ± 0.24*	13.30 ± 0.20*
	40	T2	2.48 ± 0.36*	2.70 ± 0.24*	2.58 ± 0.26*	2.10 ± 0.34*	9.86 ± 0.32*

Note: *$P<0.01$, compared with the data at T0 in the same group

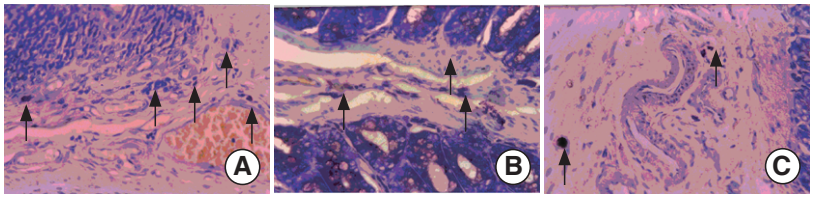

Figure 1. Comparison of MCs Activation between Groups

Notes: A: pre-treatment; B: post-treatment of the control group; C: post-treatment of the intervention group; the arrows showed the activated MCs

Table 3. Comparison of Number of Activated MCs between Groups (Cell/field, $\bar{x} \pm s$)

Group	Case	No. of activated MC	
		Pre-treatment	Post-treatment
Intervention	6	8.29 ± 0.76	3.21 ± 0.65*△
Control	6	8.02 ± 0.89	7.80 ± 0.75

Notes: *P<0.01, compared with pre-treatment in the same group; △P<0.01, compared with post-treatment of the control group

of TXYF, white atractylodes rhizome could supplement Pi and eliminate dampness; white peony root is used to regulate qi for eliminating dampness, awakening Pi and harmonizing Wei (胃); saposhnikovia root could dispel stagnancy in Gan to stretch Pi-qi, with function of drying up dampness to assist anti-diarrhea. They act together and could disperse the stagnant Gan-qi to strengthen Pi.

Modern study has found that white atractylodes rhizome mainly contains volatile oil, accounting for about 1.5%. In small doses it could raise the tension of the small intestine *in vitro* and show mild influence on contraction, but could induce the intestinal dilation in large doses[7]. White peony root, with active components of paeoniflorin, has apparent analgesia and sedative actions, could reduce the spontaneous contraction and tension of isolated intestine of guinea pigs, antagonize barium chloride-induced intestinal spasm, but shows no evident effect on that induced by acetylcholine[8]. Tangerine peel mainly contains volatile oil (1.5%-4.0%) and hesperidins (6.35%-9.93%). Its volatile oil and water extract have been proved by animal experiments to have definite inhibition on the spontaneous motion of gastrointestinal smooth muscles, and could evidently antagonize intestinal contraction or spasm induced by acetylcholine[9]. Saposhnikovia root mainly contains volatile oil, and could obviously inhibit *in vitro* intestinal muscular contraction in rabbits to dilate the spasm, which might be related to the analgesia action of the drug[10]. In sum, the whole formula could effectively inhibit the motion of the intestinal tract to slow its peristalsis, and thus cure the abdominal pain.

This study preliminarily proved the functions of TXYF in alleviating abdominal pain and distension, recovering the normal property and shape of stool, reducing the frequency of defecation, and improving tense and depressed mental conditions in IBS patients, showing that TXYF is an effective recipe for relieving patients' symptoms, and could reduce the cost for medical service for IBS patients. The possible mechanism of TXYF in treating D-IBS might be through lowering the visceral sensitivity by regulating MCs activation. However, the long-term therapeutic effect should be further observed in larger samples, and its mechanism of action needs to be further explored by molecular biological techniques like RT-PCR.

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