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Original Article

A randomized controlled trial on itopride in the treatment of patients with irritable bowel syndrome with diarrhea accompanied by abdominal distension

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Abstract: Objective: This study aims to observe the efficacy of itopride on patients with irritable bowel syndrome with diarrhea (IBS-D) accompanied by abdominal distension. Methods: Eighty patients with IBS-D accompanied by abdominal distension were randomized into an observation group and a control group (n=40, each group). The clinical symptoms, efficacy, quality of life, negative emotions and mental health of patients after treatment were observed and compared between the two groups. Results: After treatment for 6 weeks, abdominal symptoms in the two groups were improved, but the improvement in the observation group was more significant than that in the control group. Compared with the control group, patients in the observation group had better efficacy and higher total effective rates (P<0.05). Physiological function (PF), role-physical (RP), social function (SF), role-emotional (RE) and bodily pain (BP) scores in the observation group were better than those in the control group (all P<0.05). In the two groups, SAS, SDS and SCL-90 scores after treatment were significantly better than those before treatment (P<0.05), and after treatment, the three scores in the observation group were significantly better than those in the control group (P<0.05). Conclusion: Itopride can relieve clinical symptoms and improve the quality of life and mental health status of patients with IBS-D accompanied by abdominal distension, so it is worthy of clinical promotion.

Keywords: Irritable bowel syndrome with diarrhea, abdominal distension, itopride, efficacy observation, quality of life

Introduction

Irritable bowel syndrome (IBS) is a common functional bowel disease in the digestive department, it is also a syndrome characterized by diarrhea, abdominal distension, abdominal pain, along with constipation or changes of stool property [1, 2]. The disease occurs with an incidence rate of 10-20% and is clinically diagnosed without obvious morphological changes and abnormalities in biochemical examination [3]. It is divided into diarrhea-predominant IBS (IBS-D), constipation-predominant IBS (IBS-C), alternating-predominant IBS (IBS-A) and uncertain-predominant IBS (IBS-U); of which IBS-D is the most common IBS and accounts for 40.84% [4]. Current studies show that IBS is related to insufficiency of colonic motility, inflammation, imbalance of intestinal flora, brain-gut axis dysfunction, and diet; but its pathogenesis remains unclear.

According to studies, the intestinal flora in patients with IBS is significantly different from that in healthy people, i.e. patients with IBS have significantly more Escherichia coli and Bacteroides, and have significantly less Bifidobacterium [5, 6]. Therefore, drugs for the regulation of intestinal flora are usually used to treat IBS. However, the increase of aerogenic bacteria can easily cause abdominal distension, and imbalanced intestinal flora can produce special

metabolites, both of which affect the brain-gut axis and result in intestinal symptoms [7]. Patients with IBS-D should be treated with drugs along with fermentable oligosaccharides, disaccharides, monosaccharides and polyol (FODMAP) in the diet [8]. In a study, the FODMAP diet relieved symptoms of IBS-D, but it increases carbohydrates and aerogenesis, thus aggravating abdominal distension of the patients [9]. Therefore, patients with IBS-D are usually accompanied by abdominal distension. A study shows that itopride as a new prokinetic agent significantly improves abdominal distension after satiety, and the incidence rate of its side effects (1.19%) is lower than that of mosapride (5.27%) [10]. Patients with IBS-D accompanied by abdominal distension were selected as research subjects in this study to observe the efficacy of itopride.

Materials and methods

General information

Altogether 80 patients with IBS-D accompanied by abdominal distension who were admitted to the digestive department of Gastroenterology, Wuxi Traditional Chinese Medicine Hospital from January 2016 to January 2018, and their samples were collected, including 46 males and 34 females who were aged 19-65 years old with an average age of 38.3±8.6 years old. The patients were randomized into the control group (consisting of 16 males and 24 females with an average age of 38.6±8.3 years old) and the observation group (consisting of 18 males and 22 females with an average age of 38.1±9.0 years old) according to random number table. The patients included signed an informed consent form, and this study was approved by the Ethics Committee of Wuxi Traditional Chinese Medicine Hospital.

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients who met the diagnostic criteria for IBS-D based on Rome IV and who were accompanied by abdominal distension [11]; (2) Patients aged 18-65 years old; (3) Patients with diarrhea and abdominal distension for more than 3 months. Exclusion criteria: (1) Those with incomplete clinical data; (2) Those allergic to drugs; (3) Those with hemorrhage of the digestive tract after medication; (4) Pregnant and lactating women; (5) Those who had taken anticholinergic drugs; (6) Those with severe malnutrition and tumors; (7) Those with severe cardiopulmonary diseases or cerebrovascular diseases; (8) Those with psychiatric disorders and those who did not cooperate.

Methods

On the basis of the FODMAP diet, patients in the control group were treated with bifidobacterium triple viable (Shanghai Xinyi Pharmaceutical Co., Ltd.) 3 times a day with 2 packs each time. On the basis of medication in the control group, patients in the observation group were treated with itopride (Laboratoires Mayoly Spindler) 3 times a day of 50 mg each time. The abdominal distension of most patients was improved after taking itopride for approximately 6 weeks, so the treatment time was defined as 6 weeks, after which the efficacy of both groups of patients was observed. No other prokinetic agents, antispasmodics and antidepressant drugs were taken during treatment.

Outcome measures

Main outcome measures: 1) Abdominal symptom scores. Diarrhea: 0 points for 1-3 times of defecation, 1 point for 4-6 times, 2 points for 7-10 times and 3 points for more than 10 times. No abdominal distension was 0 points; mild, moderate and severe abdominal distension was 1, 2 and 3 points, respectively. No abdominal pain was 0 points; mild, moderate and severe abdominal pain was 1, 2 and 3 points, respectively. 2) Efficacy. Excellent: The clinical symptoms were improved after treatment. Effective: The symptoms were partially improved after treatment. Invalid: The symptoms were not improved and even aggravated after treatment. The total effective rate = (cured cases + excellent cases + effective cases)/total cases. 3) SF-36 Quality of Life Questionnaire (the MOS item short-form health survey) [12]. The questionnaire consisted of general health (GH), mental health (MH), physiological function (PF), role-physical (RP), social function (SF), role-emotional (RE), bodily pain (BP) and vitality (VT).

Secondary outcome measures: 1) Depression and anxiety. The Self-Rating Depression Scale (SDS) and Self-Rating Anxiety Scale (SAS) were respectively used to evaluate patients' depression and anxiety [13]. The higher the score was,

Table 1. Comparison of general information

	Observation group (n=40)	Control group (n=40)	χ^2/t	P
Age (year)	38.1±9.0	38.6±8.3	0.233	0.817
Gender			0.205	0.651
Male	18	16		
Female	22	24		
Diarrhea	2.20±0.76	2.05±0.81	0.852	0.397
Abdominal pain	2.38±0.63	2.32±0.66	0.348	0.729
Abdominal distension	2.05±0.75	2.02±0.83	0.141	0.888
Fecal character	3.88±1.26	3.96±1.12	0.187	0.852
GH	72.25±4.34	72.26±4.01	0.107	0.874
MH	89.41±3.01	89.26±2.94	1.147	0.684
PF	70.95±3.04	71.36±3.01	0.362	0.451
RP	60.41±6.13	59.21±6.24	1.248	0.532
SF	68.23±5.21	67.36±5.84	1.458	0.421
RE	60.58±5.69	59.67±5.95	1.541	0.436
BP	34.62±4.26	34.26±4.21	0.159	0.789
VT	85.69±3.54	86.14±3.47	1.145	0.694

Note: GH, general health; MH, mental health; PF, physiological function; RP, role-physical; SF, social function; RE, role-emotional; BP, bodily pain; VT, vitality.

Table 2. Comparison of abdominal symptom scores

	Observation group (n=40)	Control group (n=40)	χ^2/t	P
Diarrhea	0.82±0.64	1.45±0.75	4.022	<0.001
Abdominal pain	0.92±0.62	1.42±0.71	3.360	0.001
Abdominal distension	0.95±0.68	1.28±0.64	2.205	0.030
Fecal character	1.92±1.23	2.98±1.07	4.072	<0.001

the more severe the anxiety and depression were. 2) Mental health status. The Symptom Checklist 90 (SCL-90) was used to evaluate patients' mental health status [14]. The score was negatively correlated with the mental health status.

Statistical methods

SPSS 17.0 was used for statistical analysis. Normality test was used for measurement data using K-S test. Measurement data conforming to normal distribution were expressed by mean ± standard deviation ($\bar{x}$ ± sd), and t test was used for comparison between groups, paired t test for comparison between before and after treatment. Count data were expressed by the number of cases/percentage (n/%), tested by Pearson chi-square and represented by chi-square. P<0.05 indicates a statistically significant difference.

Results

Comparison of general information

There was no difference between the two groups in age, gender, abdominal symptom scores or quality of life scores, which were not comparable (P>0.05). More details are shown in **Table 1**.

Comparison of abdominal symptom scores

After treatment for 6 weeks, abdominal symptoms in the two groups were improved, but the improvement in the observation group was more significant than that in the control group (P<0.05). More details are shown in **Table 2** and **Figure 1**.

Comparison of efficacy

After treatment, the markedly effective, effective, invalid and total effective cases in the observation group were 18 (45.0%), 18 (45.0%), 4 (10.0%) and 36 (90.0%), respectively, and those in the control group were 9 (22.5%), 20 (50.0%), 11 (27.5%) and 29 (72.5%), respectively. There were statistically significant differences between the two groups in terms of efficacy (Z=2.498, P=0.013) and total effective rate (χ^2=4.021, P=0.045) (P<0.05). More details are shown in **Figure 2**.

Comparison of quality of life

After treatment for 6 weeks, PF, RP, SF, RE and BP scores in the observation group were 90.05±2.81, 76.73±6.46, 85.35±5.46, 79.65±6.22 and 37.18±4.03 points, respectively, and those in the control group were 74.19±3.17, 65.85±6.15, 73.35±5.46, 66.81±9.87 and 32.14±4.28 points, respectively (P<0.05). The five scores in the observation group were better than those in the control group, but there was no statistically significant difference between the two groups with respect to GH, MH or VT

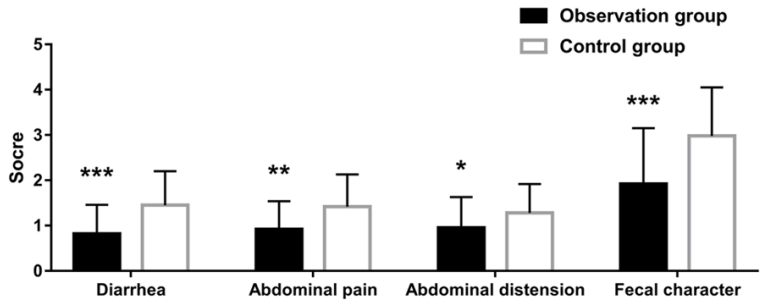

Figure 1. Comparison of abdominal symptom scores. Compared with control group, *P<0.05, **P<0.01, ***P<0.001.

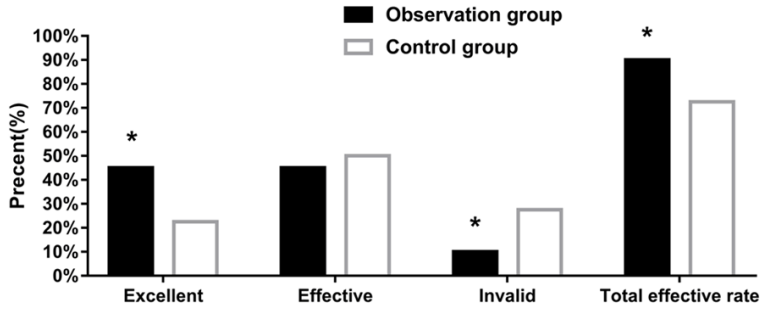

Figure 2. Comparison of efficacy. Compared with control group, *P<0.05.

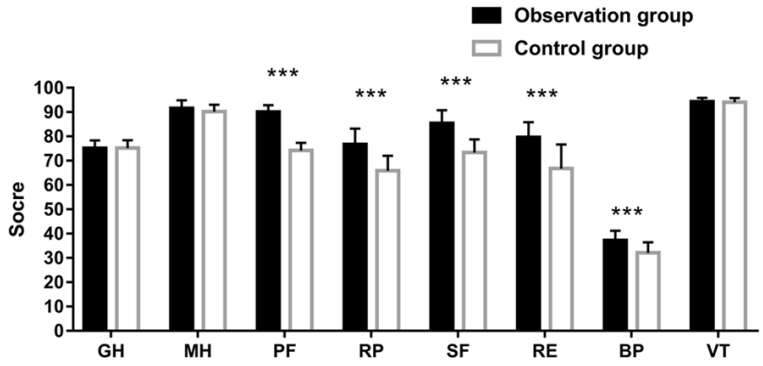

Figure 3. Comparison of quality of life. Compared with control group, ***P<0.001. GH, general health; MH, mental health; PF, physiological function; RP, role-physical; SF, social function; RE, role-emotional; BP, bodily pain; VT, vitality.

scores (P>0.05). More details are shown in **Figure 3**.

Comparison of SAS and SDS scores

Before treatment, there was no difference in SAS or SDS scores between the two groups (P>0.05), while after treatment, the two scores in both groups were significantly better than those before treatment (P<0.05), and the scores in the observation group were better than those in the control group (P<0.05). More details are shown in **Tables 3**, **4**.

Comparison of SCL-90 score

Before treatment, there was no difference in SCL-90 score between the two groups (P>0.05), while after treatment, the score in both groups was significantly better than that before treatment (P<0.05), and the score in the observation group was better than that in the control group (P<0.05). More details are shown in **Table 5**.

Discussion

IBS is a common clinical disease and patients with IBS-D account for the majority of IBS. A previous study shows that the intestinal flora in patients with IBS-D is imbalanced and different from that in healthy people, so imbalance of intestinal flora is believed to be closely related to IBS-D [15]. Changes of intestinal flora lead to immune and inflammatory responses of the intestinal mucosa, visceral hypersensitivity and abnormal gastrointestinal motility, so patients with IBS-D suffer from diarrhea and abdominal pain [16]. In a study on gastrointestinal flora in germ-free mice, germ-free conditions are more likely to develop into visceral hypersensitivity, thus causing stronger perception of pain [17]. In other studies, the transplantation of fecal microbiota from patients with IBS into germ-free mice causes pain hypersensitivity and colonic visceral hypersensitivity, as well as intestinal inflammations [18, 19]. A domestic study shows that the increased Escherichia coli is positivly related to the abdominal distension and pain in patients with IBS (r=0.457, P<0.001)

Table 3. Comparison of SDS scores

	Before treatment	After treatment	t	P
Observation group (n=40)	56.31±10.38	42.38±8.62	8.098	0.001
Control group (n=40)	56.69±10.37	49.69±9.87	4.287	0.015
T	0.697	3.365		
P	0.526	0.021		

Note: SDS, self-rating depression scale.

Table 4. Comparison of SAS scores

	Before treatment	After treatment	t	P
Observation group (n=40)	60.48±11.25	43.72±8.12	10.283	0.000
Control group (n=40)	61.12±11.62	50.21±9.14	7.298	0.009
T	0.598	3.698		
P	0.632	0.016		

Note: SAS, self-rating anxiety scale.

[20]. According to studies, defecation frequency of patients is significantly improved after regulation of the intestinal flora [5, 21]. Therefore, Bifidobacterium and lactobacillus acidophilus are commonly used for the treatment of intestinal flora.

The latest research shows that the FODMAP diet could improve the symptoms of the patients [22]. Regulation of intestinal flora and diet control significantly improve diarrhea and abdominal pain, but the increased aerogenic bacteria; and the FODMAP diet increases the intake of carbohydrates and aerogenesis, thus aggravating abdominal distension of patients with IBS-D [8, 9]. In a prospective, multi-center, phase IV clinical study, the effective rate of itopride (73%) was higher than that of other prokinetic agents (63%) for the improvement of abdominal distension [23]. In a prospective multi-center study from China, the total symptom score before and after treatment by itopride was -5.62±3.27 points, which was reduced by (69.23±26.53)% compared with baseline [24]. Therefore, itopride was used in this study to improve intestinal peristalsis function, promote defecation and exsufflation and reduce defecation frequency, thereby relieving abdominal pain, diarrhea and abdominal distension. The treatment time was 6 weeks, because some patients began to take effect 2 weeks after treatment, and patients' symptoms began to be improved 4 weeks after treatment, and the efficacy became better 6 weeks after treatment. After treatment for 6 weeks, diarrhea, abdominal pain, abdominal distension and fecal properties in the two groups were improved, but the improvement in the observation group was more significant than that in the control group.

According to studies, approximately 50% of patients with IBS suffer from anxiety and depression due to the recurrence of the disease and the aggravation of conditions, and patients with psychological diseases are more likely to develop IBS [25-27]. Anxiety, depression, diarrhea, abdominal distension, abdominal pain and abnormal defecation greatly affect patients' quality of life. In this study, after treatment for 6 weeks, PF, RP, SF, RE and BP scores in the observation group were better than those in the control group, but there was no statistically significant difference between the two groups with respect to GH, MH or VT scores. In the two groups, SAS, SDS and SCL-90 scores after treatment were significantly better than those before treatment, whereas after treatment, the three scores in the observation group were better than those in the control group. This is possibly because itopride improves patients' diarrhea, abdominal pain, abdominal distension and fecal properties, as well as their anxiety, depression and mental health status.

There are deficiencies in this study. For example, a multi-center study was not conducted, the source of cases was single and the sample size was small. Therefore, the sample size should be enlarged and a multi-center study should be conducted in a later period.

In conclusion, itopride can relieve the clinical symptoms and improve the quality of life and mental health status of patients with IBS-D accompanied by abdominal distension, so it is worthy of clinical promotion.

Disclosure of conflict of interest

None.

Table 5. Comparison of SCL-90 score

	Observation group (n=40)	Control group (n=40)	t	P	Observation group (n=40)	Control group (n=40)	t	P
	Before treatment	Before treatment			Difference	Difference		
Somatization	2.49±0.51	2.53±0.45	0.968	0.378	0.77±0.44[a]	0.40±0.23[a]	3.745	0.027
Mental disease	2.13±0.37	2.13±0.35	0.584	0.654	1.02±0.84[a]	0.21±0.12[a]	4.426	0.021
Paranoid state	2.16±0.34	2.14±0.31	0.869	0.512	0.93±0.36[a]	0.21±0.14[a]	5.261	0.002
Fear	2.34±0.57	2.31±0.51	0.802	0.562	0.90±0.36[a]	0.31±0.27[a]	3.125	0.041
Hostile	2.26±0.48	2.24±0.47	0.658	0.502	0.95±0.32[a]	0.18±0.15[a]	3.515	0.030
Anxiety	2.17±0.42	2.16±0.39	0.854	0.514	0.85±0.18[a]	0.13±0.11[a]	4.438	0.019
Depression	2.63±0.61	2.62±0.53	0.703	0.575	0.82±0.32[a]	0.33±0.25[a]	3.154	0.035
Interpersonal sensitivity	2.43±0.47	2.40±0.45	0.603	0.674	0.93±0.35[a]	0.30±0.11[a]	4.024	0.014
Obsessive-compulsive	2.76±0.62	2.71±0.53	0.584	0.641	1.15±0.41[a]	0.67±0.23[a]	3.362	0.024

Note: Compared with before treatment, [a]P<0.05.

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