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Original Article

Effect of probiotics and dietary fiber combined with pinaverium bromide on intestinal flora in patients with irritable bowel syndrome

Han Sun, Xueting Li, Weixu Chen, Fangyuan Jia, Jing Su, Bao Zhang, Xia Wu, Ping Wu

Department of Gastroenterology, Xuzhou Central Hospital, Xuzhou, China

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Abstract: Objective: To evaluate the clinical efficacy of probiotics and dietary fiber combined with pinaverium bromide in the treatment of irritable bowel syndrome (IBS) and its effect on intestinal flora. Methods: As a prospective study, 180 patients with IBS hospitalized in the gastroenterology department of our hospital from January 2018 to January 2021 were selected and assigned to Group A, Group B, or Group C using the random number table method, with 60 cases in each group. Patients in Group A received conventional treatment with pinaverium bromide tablets. Those in Group B were given bifid triple viable combined with pinaverium bromide, and those in Group C were given bifid triple viable and dietary fiber combined with pinaverium bromide. The treatment spanned 4 weeks. The treatment efficacy, degree of symptom improvement, quality of life, adverse effects, and changes in intestinal flora were compared among the three groups. Results: The total treatment efficacy was significantly higher in Group C compared with Group A (χ^2=8.711, P=0.003), while it differed insignificantly between Group A and Group B (P>0.05). Groups B and C had a shorter resolution time of abdominal pain, diarrhea, and abdominal distension than Group A (P<0.05). Compared with Group B, Group C experienced a markedly shorter resolution time of abdominal pain (P<0.05). The IBS symptom severity scale (IBS-SSS) and IBS-quality of life (IBS-QOL) scores were the lowest in Group C, followed by Group B, and then Group A (P<0.05). Group A had a significantly higher E. coli count and lower Bifidobacterium and Lactobacillus counts than Groups B and C (P<0.05). Adverse reactions were all within the tolerable range in the three groups, with no difference (P>0.05). Conclusion: In patients with IBS, treatment with probiotics and dietary fiber combined with pinaverium bromide can significantly improve clinical efficacy, shorten symptom resolution time, reduce calprotectin, and regulate intestinal flora.

Keywords: Irritable bowel syndrome, probiotics, dietary fiber, pinaverium bromide, intestinal flora

Introduction

Irritable bowel syndrome (IBS) is a group of intestinal disorders characterized by persistent or intermittent episodes of abdominal pain, abdominal distention, altered bowel movements, and/or changed stool characteristics, without structural and biochemical abnormalities of the gastrointestinal tract [1, 2]. The etiology and pathogenesis of IBS are still poorly understood, but its onset is considered to be associated with contributory factors such as abnormal gastrointestinal motility, abnormal visceral sensation, abnormal brain-gut regulation, inflammation, and psychosomatic factors [3, 4]. The current treatment of IBS is committed to symptomatic management to eliminate patients' concerns, alleviate symptoms, and enhance the quality of life. The principles of treatment are based on a positive doctor-patient relationship, symptom treatment depending on the main symptom type, and graded treatment corresponding to the severity of symptoms, with attention devoted to the individualization and integrated use of treatment measures. Treatment mainly includes diet instruction, psychological and behavioral therapy, and medication.

In the treatment of IBS, selective calcium channel blockers are widely used to relieve abdominal pain and distension of the intestine through direct antispasmodic effects [5]. Pivetonium bromide is an antispasmodic agent that acts in the gastrointestinal tract and is also a calcium antagonist that inhibits the influx of calcium

ions into the smooth muscle cells of the intestine. Pivetonium bromide is the first antagonist with a highly selective antispasmodic effect on the gastrointestinal tract primarily for the treatment of abdominal pain, bowel disorders, intestinal discomfort associated with irritable bowel syndrome, as well as pain associated with functional intestinal disorders and preparation for barium enema. However, it is criticized for poor absorption and rapid metabolism when taken orally. Drug therapy fails to exert a radical amelioration of the intestinal condition of patients who are also predisposed to recurrence [6].

Exacerbation of IBS symptoms is primarily ascribed to poor eating habits and dietary structure, which highlights the significance of dietary modification as a main therapeutic approach for the treatment of IBS [7]. Intestinal microecological imbalance and changes in the intestinal environment may be associated with the development and persistence of IBS symptoms. Probiotics are a class of microecological agents that maintain intestinal microbial homeostasis by protecting both beneficial and pathogenic bacteria, which have been extensively adopted in the treatment of diarrheal IBS [8]. Probiotics are closely associated with the epithelial cells of the intestinal mucosa through phosphopeptidic acid, and together with other anaerobic bacteria form a biologic protective barrier on the surface of the intestinal mucosa to strengthen the defensive capacity of the epithelial cells. A series of chemicals, such as its metabolites, also form a chemical protective barrier to prevent the implantation and invasion of harmful flora. Inflammatory lesions in the human intestine are mostly accompanied by more or fewer flora disorders and dysbiosis, resulting in a strong immune response, which tends to aggravate the imbalance of flora and the variations of the conditions. The use of probiotics to stabilize the intestinal flora can cut off this vicious cycle and restore the normal peristaltic function of the intestine. Dietary fiber is effective in enhancing stool quality and shortening intestinal transport time to further mitigate diarrhea and constipation symptoms in patients [9]. High dietary fiber can promote intestinal motility, which is favorable for patients with irritable bowel syndrome of constipation type. However, the combined application of probiotics and dietary fiber in the treatment of IBD has been reported less frequently. Accordingly, this study evaluated the clinical efficacy and safety of probiotics and dietary fiber in combination with pinaverium bromide in the treatment of IBS.

Materials and methods

General information

As a prospective study, 180 patients with IBS treated in the gastroenterology department of our hospital from January 2018 to January 2021 were selected and assigned to Group A, Group B, or Group C using the random number table method, with 60 cases in each group. The hospital ethics committee approved the study protocol (approval number: CL2019-12021) and the study was conducted in accordance with the principles of medical research and the *Declaration of Helsinki* [10].

Inclusion and exclusion criteria

Inclusion criteria

(1) Patients aged 18 to 70 years old; (2) Patients who met the diagnostic criteria for IBS [11]; (3) Patients who signed the informed consent form after being fully informed of the purpose and process of the study.

Exclusion criteria

(1) Patients with organic intestinal diseases, such as inflammatory bowel disease, intestinal tuberculosis, malabsorption syndrome, celiac disease, and lactose intolerance; (2) Patients with a history of abdominal and pelvic surgery, such as cholecystectomy; (3) Patients with non-intestinal diseases of the digestive system, such as chronic pancreatitis, tumors, peptic ulcers, tuberculous peritonitis, chronic liver disease, and cirrhosis; (4) Patients with other serious diseases, including serious lesions of vital organs such as the heart, lungs, and kidneys, immunomodulatory diseases, and metabolic diseases; (5) Patients with current, recent (within 1 month), or long-term use of microecological preparations, dietary supplements or herbal medicines, or high doses of vitamins or minerals; (6) Patients with current, recent (within 1 month), or long-term use of antibiotics; (7) Patients who were unable to cooperate in completing the study investigation, including difficulties in follow-up and communication impairment due to severe mental illness; (8) Pregnant or lactating women or women of childbearing age who were preparing for pregnancy.

Treatment methods

Group A was given oral pinaverium bromide tablets (Manufacturer: Beijing Wansheng Pharmaceutical Co. LTD, Approval Number: H20-133036), 40 mg/dose, 3 times/day. On the basis of Group A, Group B was additionally given Bifodanbifid triple viable (Manufacturer: Bifodan A/S Co. LTD, Approval Number: JY13-101160095303) 1 g/dose, 1 time/day. Group C was supplemented with oral Qingyijian (dietary fiber) 6 g/dose once a day on the basis of Group B. The treatment spanned 4 weeks.

Outcome measures

Primary outcome

Clinical efficacy: Classification of patients' clinical efficacy was performed according to their main symptoms (abdominal pain, bloating, and defecation). Grade 0: Patients with no symptoms or disappearance of all symptoms; Grade 1: patients with symptoms that were detected after being prompted; Grade 2: Patients with obvious symptoms that did not disrupt daily life and work; Grade 3: Patients with obvious symptoms that disrupted daily life and work. If all clinical symptoms disappeared, the treatment efficacy was considered markedly effective. If the symptoms were ameliorated by more than 2 grades after treatment, the treatment efficacy was considered effective. If the symptoms were ameliorated by less than 2 grades after treatment, the treatment efficacy was considered ineffective. Total efficacy = (number of effective cases + number of markedly effective cases)/total number of cases.

Secondary outcomes

Time of symptom resolution: The patients were followed up and the resolution time of abdominal pain, bloating, and diarrhea was recorded.

Symptom scores

The IBS symptom severity scale (IBS-SSS) [12] was used to assess the severity of the patients' symptoms, including the severity of abdominal pain, frequency of abdominal pain, severity of abdominal distension, dissatisfaction with bowel habits, and quality of life. The IBS-SSS was graded according to the severity of bowel symptoms, with a score of 75-175 for mild bowel symptoms, 175-300 for moderate bowel symptoms, and >300 for severe bowel symptoms.

Quality of life scores

The IBS-quality of life (IBS-QOL) [13] scale, which includes 34 items with each item divided into 5 levels of 1 to 5 points, was used to assess patients' quality of life from 8 domains, including mood, daily activities, personal image, diet, health concerns, sexual behavior, and interpersonal relationships. The scores were summed and then converted to percentages, with lower scores indicating better quality of life.

Intestinal flora

Stool samples were collected before treatment and four weeks after treatment in both groups. Fresh stool (1 g) was collected with a sterile cotton swab, diluted with 1 mL saline, shaken, and mixed on an oscillator, and diluted into a series with diluent at a 10-fold dilution rate. The above treated specimen series dilutions of 0.01 mL were taken and inoculated onto the surface of the various selective media above and incubated at 37°C for 72 h, followed by the counting of colonies growing on the surface of each dilution after incubation. Lactobacillus and Bifidobacterium were identified from a certain number of colonies randomly selected in each medium according to their biologic characteristics and biochemical response characteristics to exclude or determine the number of colonies. Logarithmic value of live bacterial colony forming unit per gram of stool (CFU/g) = (specimen mass (g) + dilution volume (mL))/ specimen mass × dilution ratio × number of colonies; the final result was calculated with the dilution ratio of 102 times.

Statistical analyses

SPSS 22.0 software was used to organize and statistically analyze the data, and GraphPad Prism software was used for image rendering. Measurement data were expressed as (mean± standard deviation/±s); ANOVA was used for comparison among multiple groups or multiple time points; and for the comparison between two groups, a post hoc test after ANOVA was adopted. Count data were expressed as rates [cases/percentages (n%)], and the chi-square test was used to verify the existence of statisti-

Table 1. Comparison of general information among the three groups

	Group A (n=60)	Group B (n=60)	Group C (n=60)	F/χ^2	P
Age (years)	34.56±6.42	36.31±7.04	35.11±7.35	0.996	0.372
Gender (male/female)	44/16	38/22	41/19	1.386	0.500
BMI (kg/m^2)	22.88±4.32	23.91±5.43	24.12±5.84	0.964	0.383
Course of disease	5.89±2.85	6.11±3.58	7.03±3.86	1.837	0.162
IBS type				2.151	0.905
Diarrhea (IBS-D)	41	38	35		
Constipation (IBS-C)	10	9	10		
Mixed type (IBS-M)	6	8	9		
Alternate type (IBS-A)	3	5	6		

Table 2. Comparison of clinical efficacy among the three groups

	Markedly effective	Effective	Ineffective	Overall effective rate
Group A (n=60)	12	26	22	38 (63.33)
Group B (n=60)	18	28	14	46 (76.67)
Group C (n=60)	20	32	8	52 (86.67)
χ^2				8.904
P				0.012

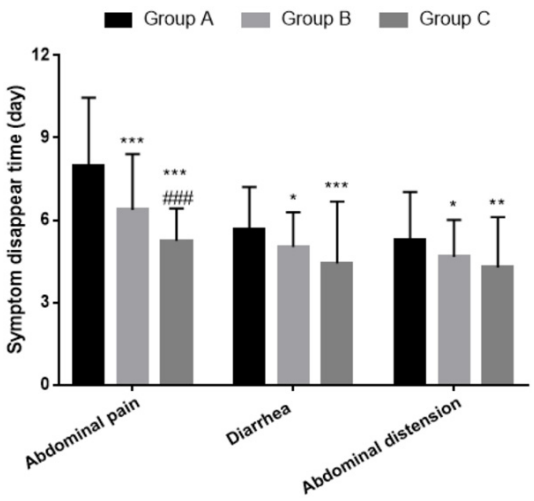

Figure 1. Comparison of symptom resolution time among the three groups. Note: *: vs Group A, P<0.05; **: vs Group A, P<0.01; ***: vs Group A, P<0.001; ###: vs Group B, P<0.001.

cal differences. The difference was considered significant at the threshold of α=0.05.

Results

Comparison of general information

The three groups presented no significant difference in general information such as age, gender, BMI, course of disease, and the type of disease (P>0.05) **Table 1**.

Comparison of clinical efficacy

As shown in **Table 2**, Group A had 12 cases that were markedly effective, 26 cases effective, and 22 cases ineffective, with an overall efficacy of 63.33% (38/60). Group B had 18 cases that were markedly effective, 28 cases effective, and 14 cases ineffective, with an overall efficacy of 76.67% (46/60). Group C had 20 cases that were markedly effective, 32 cases effective, and 8 cases ineffective, with an overall efficacy of 86.67% (52/60). The inter-Group comparison revealed a significantly higher total efficacy in Group C compared with Group A (χ^2=8.711, P=0.003), while no significant difference was observed between groups A and B (P>0.05).

Comparison of symptom resolution time

Groups B and C had a shorter resolution time of abdominal pain, diarrhea, and abdominal distension than Group A (P<0.05), and compared with Group B, Group C experienced a markedly shorter resolution time of abdominal pain (P< 0.05). No significant difference was observed in terms of the resolution time of diarrhea and abdominal distension between Group B and Group C (P>0.05) **Figure 1**.

Comparison of IBS-SSS scores

Before treatment, the three groups showed no significant difference in IBS-SSS scores (P>0.05). After treatment, the IBS-SSS score was the lowest in Group C, followed by Group B and Group A (P<0.05) **Table 3**.

Table 3. Comparison of IBS-SSS among the three groups

Group	Before treatment	After treatment	t	P
Group A (n=60)	322.36±66.28	192.05±38.18	13.20	<0.001
Group B (n=60)	318.28±59.75	175.25±32.58*	16.28	<0.001
Group C (n=60)	330.14±68.45	142.32±35.68***,###	18.85	<0.001
F	0.517	30.38		
P	0.597	<0.001		

Note: *: vs Group A, P<0.05; ***: vs Group A, P<0.001; ###: vs Group B, P<0.001.

Table 4. Comparison of IBS-QOL scores among the three groups

Groups	Before treatment	After treatment	t	P
Group A (n=60)	48.28±10.53	32.84±8.57	8.809	<0.001
Group B (n=60)	51.03±12.42	29.19±7.48*	11.67	<0.001
Group C (n=60)	53.29±13.87	25.45±5.82***,##	14.34	<0.001
F	2.477	15.05		
P	0.087	<0.001		

Note: *: vs Group A, P<0.05; ***: vs Group A, P<0.001; ##: vs Group B, P<0.001.

Table 5. Comparison of intestinal flora among the three groups

Groups	E. coli	Bifidobacterium	Lactobacillus
Group A (n=60)	8.58±2.54	7.28±2.39	6.14±1.25
Group B (n=60)	7.33±2.15**	9.28±2.45***	6.87±1.52**
Group C (n=60)	7.25±2.26**	10.21±3.24***	7.01±1.68**
F	6.188	18.17	5.867
P	0.003	<0.001	0.003

Note: **: vs Group A, P<0.01; ***: vs Group A, P<0.001.

Table 6. Comparison of adverse reactions among the three groups

Groups	Dry mouth	Nausea and vomiting	Dizziness and insomnia	Total incidence rate
Group A (n=60)	3	2	1	6 (10.00)
Group B (n=60)	4	1	2	7 (11.67)
Group C (n=60)	3	2	3	8 (13.33)
χ^2				0.324
P				0.851

Comparison of IBS-QOL scores

As shown in **Table 4**, no significant difference was observed in the IBS-QOL score among the three groups before treatment (P>0.05). After treatment, Group C had the lowest IBS-QOL scores, followed by Group B and Group A (P<0.05).

Comparison of intestinal flora

Group A had a significantly higher E. coli count and lower Bifidobacterium and Lactobacillus counts than groups B and C (P<0.05). The counts of intestinal flora in Group B were similar to those in Group C (P>0.05) **Table 5**.

Comparison of adverse reactions

After treatment, Group A had 3 cases of dry mouth, 2 cases of nausea and vomiting, and 1 case of dizziness and insomnia, with a total incidence of adverse reaction of 10.00% (6/60). Group B had 4 cases of dry mouth, 1 case of nausea and vomiting, and 2 cases of dizziness and insomnia, with a total incidence of adverse reaction of 11.67% (7/60). Group C had 3 cases of dry mouth, 2 cases of nausea and vomiting, and 3 cases of dizziness and insomnia, with a total incidence of adverse reactions of 13.33% (8/60). Adverse reactions were all within the tolerable range in the three groups, with no significant difference among the three groups (P>0.05) **Table 6**.

Discussion

IBS is a group of intestinal disorders characterized by persistent or intermittent episodes of abdominal pain, abdominal distention, and changes in bowel habits and/or stool characteristics, without structural and biochemical abnormalities of the gastrointestinal tract. People aged 20-50 years old are susceptible to the disease, with a higher morbidity in females than males [14]. IBS occurs in times of emotional stress and environmental change, which compromises patients' quality of life and even leads to extra-gastrointestinal symptoms such as anxiety, depression, and sleep disturbances in severe cases [15]. In this study, probiotics and dietary fiber combined with pinaverium

bromide significantly improved the clinical efficacy, shortened the symptom resolution time, and raised the quality of life of patients.

The occurrence and development of IBS are closely associated with dysbiosis of the intestinal flora. Research has shown that the ectopic intestinal flora of patients with IBS leads to changes in the dominant flora in the small intestinal, which triggers dysbiosis and compromises the nutrient absorption function of the intestine [16]. Oral probiotics regulate the beneficial intestinal flora, thereby relieving abdominal discomfort. Bifodan® GI PULS is manufactured by Bifodan Corporation of Denmark and contains three superior probiotic strains, namely, Bifidobacterium animalis BIFOLAC™ 12, Lactobacillus acidophilus BIFOLAC™ 5, and Lactobacillus acidophilus BIFOLAC™ 5. The superior probiotic strain isolated from the human body has strong acid, bile, and antibiotic resistance, with an initial live bacterial content of 1.5×10^{10} CFU per gram, which, after a shelf life of up to 24 months, still remains 2×10^{9} CFU per gram. Herein, Group A had a significantly higher E. coli count and lower Bifidobacterium and Lactobacillus counts than Groups B and C ($P<0.05$), indicating that the combined use with probiotics maintains a stable intestinal flora which is a primary reason for their effectiveness. Konstantinos et al. compared the efficacy of Saccharomyces boulardii, Bifidobacterium lactis, Lactobacillus acidophilus, and Lactobacillus plantarum in IBS and confirmed that for certain symptoms in patients with diarrheal and constipated irritable bowel syndrome, the intake of probiotics significantly improved the clinical outcome of patients, which was consistent with the results of the present study [17].

Dietary fiber is a polysaccharide, which is a indigestible component of plant cell walls that is of no nutritional value. Its importance has long been underestimated. There is growing evidence that dietary fiber acts as a prebiotic and influences the composition of the intestinal flora. In addition, the byproducts of dietary fiber lower the intestinal pH and thus promote the growth of beneficial bacteria such as lactobacilli and bifidobacteria. Research has shown that insoluble fiber cannot be decomposed by intestinal microorganisms, and its application in patients with IBS is promising as it can increase stool volume lines, accelerate colonic transport, and shorten intestinal transport time in patients with constipation [18]. It has been demonstrated that insoluble fiber cannot be decomposed by intestinal microorganisms, and its application in IBS patients is considered promising, as it increases stool volume, accelerates colonic transport, and shortens intestinal transport time in patients with constipation [18]. Qingyijian is a fibrous solid drink mainly composed of round-bud psyllium husk and rich in dietary fiber, which contributes to the prevention and treatment of constipation or diarrhea [19]. It fully absorbs water, increases stool volume to excretable masses, facilitates intestinal motility, and shortens the fecal transport time in the intestine, to ensure regular defecation. Previous research suggests that dietary fiber may serve to alleviate the overall symptoms of patients with irritable bowel syndrome, abdominal discomfort/pain, bloating/bulking, and altered bowel habits, with possible relevance to the modulation of NES [20]. In this study, the combination of dietary fiber significantly reduced the IBS-SSS and shortened the resolution time of abdominal pain compared with the treatment without dietary fiber, which provides an evidence-based medical basis for its application in the treatment of IBS.

The limitations of this study are as follows. First, there are psychological factors that influence disease progression and treatment in IBD, and the patients in this study were not blinded as to the medications they were taking, which may considerably interfere with the evaluation of efficacy. Second, the high recurrence rate of IBD and the short follow-up period of this study prevented the comparison of the long-term outcomes of the two groups of patients. Finally, this study is a small sample single-center study whose results may be inconclusive to confirm definite efficacy.

In conclusion, probiotics and dietary fiber combined with pinaverium bromide in the treatment of patients with IBS can significantly improve clinical efficacy, shorten symptom resolution time, reduce calprotectin, and regulate intestinal flora.

Disclosure of conflict of interest

None.

Address correspondence to: Ping Wu, Department of Gastroenterology, Xuzhou Central Hospital,

Xuzhou, China. Tel: +86-18952171618; E-mail: wuping19638@126.com

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