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Original Article

Clinical efficacy and gastrointestinal hormonal effect of *Lactobacillus rhamnosus* combined with lactulose for treatment of irritable bowel syndrome with constipation

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Abstract: Objective: This study aimed to explore the clinical efficacy of *Lactobacillus rhamnosus* combined with lactulose for the treatment of irritable bowel syndrome with constipation (IBS-C) and its effect on gastrointestinal hormones. Methods: A prospective, randomized, double-blind trial was conducted with three groups: control (n=45, mosapride citrate tablets), monotherapy (n=44, lactulose + control regimen), and combination (n=45, Lactobacillus rhamnosus + monotherapy regimen). The primary outcome measure was clinical efficacy. Secondary outcomes included the Bristol Stool Scale (BSS), Irritable Bowel Syndrome Quality of Life Score (IBS-QoL), Perceived Stress Scale (PSS), Irritable Bowel Syndrome Severity Score (IBS-SSS), gut microbiota, and gastrointestinal hormones assessed at days 0, 28, and 56, along with safety observations. Results: Following a 56-day intervention period, the combination group achieved 100.00% clinical effectiveness, significantly higher than the monotherapy (93.18%) or control groups (75.56%). Fecal consistency responders were 84.44% in the combination group vs. 47.73% (monotherapy) and 28.89% (control). The combination group showed higher IBS-QoL scores, lower PSS scores, and reduced IBS-SSS scores ($P < 0.05$). Intestinal flora analysis revealed decreased Ruminococcaceae and increased Fibrobacteraceae and Campylobacteraceae in the combination group. Gastrointestinal hormones improved, with increased motilin and decreased vasoactive intestinal peptide ($P < 0.05$). There was no significant difference in the incidence of adverse events among the three groups ($P > 0.05$). Conclusion: *Lactobacillus rhamnosus* combined with lactulose significantly improves IBS-C symptoms and quality of life, and positively modulates intestinal flora and gastrointestinal hormones.

Keywords: Lactobacillus rhamnosus, lactulose, irritable bowel syndrome with constipation, gastrointestinal hormones

Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder caused by a variety of factors. It has a prevalence of 9% to 16% in the general population, with a slightly higher prevalence in women [1]. The predominant symptoms of IBS include abdominal discomfort, episodes of diarrhea or constipation, and alterations in bowel habits. It is generally classified into four subtypes: diarrhea-predominant, constipation-predominant, mixed, and unspecified [2]. Among these, irritable bowel syndrome with constipation (IBS-C) is the most common manifestation. Patients often experience abdominal discomfort, bloating, and pain, which seriously affect their quality of life, reduce work and study efficiency, and impose a significant burden on their physical and mental health [3]. With the rapid pace of modern life, changes in the social environment, and alterations in diet and lifestyle, the prevalence of IBS-C is increasing annually. Currently, a wide range of medications is available for the clinical treatment of IBS-C, including antispasmodics, analgesics, stimulant laxatives, osmotic laxatives, lubricant laxatives, and bulk-forming laxatives [4]. However, long-term use of these drugs may lead to dependence and can cause a series of side effects, such as gastrointestinal bloating, electrolyte imbalances, mechanical intestinal paralysis, and intestinal obstruction [5]. Therefore, there is an urgent need for a safer and more effective treatment option to alleviate symptoms and improve patients' quality of life.

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Lactobacillus rhamnosus, a type of probiotic, can alleviate symptoms in IBS patients by modulating the intestinal microbiota balance, suppressing the proliferation of harmful bacteria, and strengthening the function of the intestinal barrier [6]. However, the efficacy of probiotics may be influenced by individual differences, such as in patients with a longer disease duration or those with other gastrointestinal diseases [7]. As an osmotic laxative, lactulose not only promotes intestinal peristalsis and improves constipation symptoms but also helps to regulate the intestinal flora by acidifying the intestinal environment. This action indirectly relieves symptoms of abdominal pain and bloating, making it particularly suitable for patients with IBS-C [8]. Nevertheless, the use of lactulose may lead to side effects such as bloating and gas accumulation, and its slow onset of action usually requires long-term use to achieve a therapeutic effect [9]. Considering the different mechanisms of action of Lactobacillus rhamnosus and lactulose in the treatment of IBS, we conjecture that a combination regimen might enhance efficacy and reduce symptoms. However, further clinical studies were needed to validate its safety and efficacy.

Gastrointestinal hormones play a crucial role in the development of IBS. Research indicates that abnormal secretion of gastrointestinal hormones may affect intestinal motor function, sensory function, and intestinal microecological responses [10]. Therefore, *Lactobacillus rhamnosus* and lactulose may further ameliorate intestinal dysfunction by regulating gastrointestinal hormone levels. In summary, this study aimed to assess the clinical efficacy of using a combination of *Lactobacillus rhamnosus* and lactulose in patients with constipation-predominant irritable bowel syndrome (IBS-C), while also examining its effects on gastrointestinal hormone levels. The goal was to provide a scientific rationale for more effective, integrated management of IBS-C.

Materials and methods

Study population and experimental design

The study was a prospective, randomized, double-blind trial involving three groups: control group (receiving mosapride citrate tablets), monotherapy group (receiving oral lactulose in addition to the control group regimen), and combination group (receiving Lactobacillus rhamnosus in addition to the monotherapy group regimen). The intervention period was 56 days. During the 14-day screening period, the researchers explained the study design in detail to the participants and obtained written informed consent in the local language, which was signed and dated by the participants. This study was approved by the Ethics Committee of Taishan Hospital of Shandong Province (No.: 202112001). This study has been registered in the Chinese Clinical Trial Registry with the registration number of ChiCTR2600123361. Throughout the study, the inclusion and exclusion criteria for all participants were rigorously assessed, and their baseline data, including age, gender, height, weight, BMI, disease duration, years of education, systolic blood pressure, diastolic blood pressure, smoking history, and alcohol consumption history, were recorded.

Sample size estimation

The sample size was determined based on the primary outcome measure, which was clinical efficacy. Based on previous studies, it was assumed that the treatment efficacy over the 56-day treatment period would be 90% in the combination group and 60% in the control group. With α=0.05 and β=0.10, the minimum sample size required was 39 cases per group. Taking into account a potential loss-to-follow-up rate of 10%-20%, 45 cases per group needed to be included. Thus, a total of 135 participants needed to be recruited for the entire study.

Participants

Participants were recruited from January 2022 to January 2024 at Taishan Hospital in Shandong Province.

Inclusion criteria: According to the 2006 Rome III criteria [11], participants had experienced symptoms of abdominal pain, bloating, and abdominal discomfort for at least 6 months, with symptoms recurring in the last 3 months. Additionally, they had at least 2 of the following symptoms for at least 3 days in each of the last 3 months: (1) Improvement of symptoms after defecation; (2) Episodes accompanied by a change in the frequency of defecation; (3) Fewer than 3 defecations per week; (4) Hard/

lumpy stools; (5) A feeling of incomplete evacuation; (6) Abdominal distension. Furthermore, the following auxiliary tests were normal: (1) Routine fecal examination, fecal culture, and fecal occult blood test; (2) Thyroid function measurement; (3) Gastrointestinal ultrasound; (4) Colonoscopy.

Exclusion criteria: (1) Organic diseases of the intestinal tract, such as intestinal cancer, intestinal tuberculosis, and ulcerative colitis; (2) Endocrine, pharmacological, or neurological causes of constipation; (3) Use of laxatives, medications affecting gastrointestinal motility, digestive enzymes, or probiotic preparations within 3 months prior to treatment.

Withdrawal and discontinuation criteria: (1) The subject voluntarily withdraws from the study and requests to exit the study. (2) Occurrence of any serious adverse event during the study period, such as intestinal obstruction, anaphylactic shock, or symptomatic hypokalemia, which, in the judgment of the investigator, renders continued participation unsuitable. (3) The subject becomes pregnant. (4) Use of medications prohibited by the study protocol during the research period. (5) Loss to follow-up, defined as failure to attend two consecutive scheduled visits with inability to make contact. (6) Any other situation where the investigator determines that continued participation may pose a risk to the subject's health.

Treatment and Blinding Implementation

All three groups of patients received basic treatment, including dietary guidance, nutritional support, and maintenance of water-electrolyte balance. Control group: Patients were administered Mosapride Citrate Tablets (Chengdu Kanghong Pharmaceutical Group Co., Ltd., National Drug Approval No. H20031110, 5 mg/tablet), 3 times daily, 1 tablet each time, taken orally 0.5 hours before meals. Concurrently, to maintain blinding, patients in this group were required to take a placebo oral liquid matched in appearance, smell, and taste to the lactulose used in the monotherapy group (composed of non-therapeutic flavored solvents), as well as a placebo powder matched to the active Lactobacillus rhamnosus powder (used in the combination group) in appearance and packaging (composed of inactive ingredients such as maltodextrin). Monotherapy group: In addition to the basic regimen of the control group, patients received lactulose oral solution (66.7 g/100 mL, manufactured by Dumex, Abbott Healthcare, USA), at a dosage of 10 mL, three times daily. Concurrently, patients in this group were required to take a placebo powder matched to the active *Lactobacillus rhamnosus* powder (used in the combination group) in appearance and packaging. Combination group: In addition to the regimen of the monotherapy group (basic treatment + lactulose), patients received *Lactobacillus rhamnosus* GG (LGG) powder (Jingchangle, produced by Zhejiang Jingxin Pharmaceutical Co., Ltd., China; containing ≥ 1.0 × 10^9 CFU/g of viable bacteria) at a dosage of 500 mg, three times daily.

To ensure the validity of the double-blind design, all study interventions (active drugs and their corresponding placebos) were uniformly coded, allocated, and packaged by independent pharmacy personnel not involved in patient recruitment, clinical evaluation, or data analysis, according to a computer-generated random sequence. All oral liquids and powders were packaged in identical, opaque containers to ensure that participants, study personnel administering the interventions, and outcome assessors remained blinded to group assignment. The taste and smell of the study products were formulated and tested to minimize detectable between groups. The group allocation code was only revealed after study completion and database lock.

Safety management and emergency procedures

All participants were closely monitored for safety throughout the trial. All adverse events (AEs) were recorded, including their type, time of onset, severity (graded according to CTCAE v5.0), duration, measures taken, and outcomes. Emergency equipment and medications were available on-site, and all study personnel were trained in emergency procedures. A predefined protocol was established for managing gastrointestinal AEs (e.g., diarrhea, abdominal cramps): mild to moderate events were managed with close observation and lifestyle guidance, while severe events (Grade ≥ 3) led to immediate temporary discontinuation of the study intervention and appropriate support-

ive care until resolution. All serious AEs were reported to the Ethics Committee within 24 hours.

Observation indicators

On days 0, 28, and 56, we assessed study outcomes, conducted clinical examinations, distributed or collected study products, and documented concomitant medication use. Clinical efficacy was evaluated only at Day 56. For patients experiencing severe abdominal pain and/or frequent loose stools, metronidazole (400 mg/day) may be administered as rescue therapy. Previous studies have demonstrated that metronidazole alleviates IBS symptoms without affecting sigmoid-rectal motility [12]. Adherence to the study product was assessed through participant-completed medication diaries and verified by counting remaining product at each visit. Participants were required to complete dietary diaries within 14 days prior to each visit, documenting food intake over two weekdays and one weekend day.

Main outcomes: Clinical efficacy: The criteria for judging the efficacy were as follows: disappearance of clinical symptoms was considered as "cure"; spontaneous bowel movement within 2 days and significant relief of constipation symptoms were considered as "marked effect"; spontaneous bowel movement within 3 days and relief of symptoms such as dry stools and abdominal pain were considered as "effective"; no change or worsening of symptoms and signs was considered as "ineffective". The total effective rate was determined by the formula: (cure + marked effect + effective)/total number of cases × 100% [13].

Secondary outcomes: Secondary outcome indicators included the following tests: the Bristol Stool Shape Scale (BSS), the Irritable Bowel Syndrome Quality of Life Score (IBS-QoL), the Psychological Stress Scale (PSS), the Irritable Bowel Syndrome Severity Scale (IBS-SSS), assessments of intestinal flora, and measurements of gastrointestinal hormones at days 0, 28, and 56. These secondary outcome indicators are detailed below: BSS: Stool consistency was assessed using the BSS, a widely recognized tool that classifies fecal types on a scale of 1 to 7. Types 1 and 2 on this scale are indicative of constipation [14]. Responders in terms of fecal consistency were defined as those who had at least one type 1-2 stool per week on more than 50% fewer days compared to baseline.

IBS-QoL: IBS-related quality of life was measured using the IBS-QoL questionnaire, which consists of 34 items, each rated on a 5-point scale (total score range: 34-170). Higher scores on this questionnaire indicate better quality of life [14].

PSS: Psychological stress was evaluated using the PSS, which consists of 10 entries on a scale of 0-40, with higher scores indicating greater perceived stress [15].

IBS-SSS: The severity of IBS symptoms was assessed using the IBS-SSS. This scale ranges from 0 to 500 and includes five separate domains (0 to 100) that evaluate the severity of abdominal pain, frequency of abdominal pain, severity of bloating, dissatisfaction with bowel habits, and impairment in quality of life. A reduction of 95 points on the scale is considered to represent a clinically significant improvement [16].

Intestinal flora: Four bacterial families, Helicobacteriaceae, Fibrobacteriaceae, Campylobacteriaceae and Rumatobacteriaceae, were enumerated using qPCR. First, total DNA was extracted from fecal samples. Specific primers targeting the 16S rRNA genes of the respective bacterial families were used for PCR amplification. SYBR Green fluorescent dye was added to the reaction system, and the DNA content of the target bacterial communities was quantified by real-time monitoring of the fluorescence signal intensity. Each sample was run in triplicate, and a standard curve was established to ensure the accuracy of quantification. The $2^{\wedge(-\Delta\Delta Ct)}$ method was employed for data analysis, normalizing the Ct values of the target bacterial communities to an internal reference gene (such as the universal bacterial 16S rRNA gene). The relative quantification results for each bacterial family were ultimately obtained.

Gastrointestinal Hormones: A fasting venous blood sample (3-5 mL) was drawn from the patients. The serum was separated by low-temperature centrifugation at 2500 rpm for 10 minutes and then stored at -70°C. The concentrations of Motilin (MTL, measured using the Fine Biotech Human Motilin ELISA Kit, China)

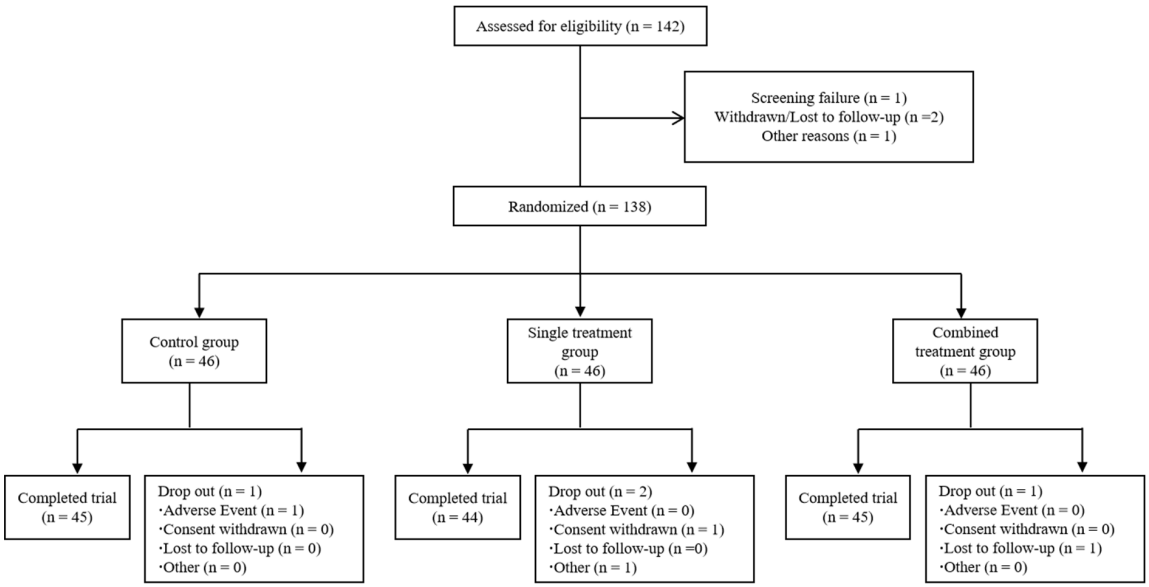

Figure 1. CONSORT flowchart of patients throughout the study.

and vasoactive intestinal peptide (VIP, measured using the Human Vasoactive Intestinal Peptide ELISA Kit, China) were determined using the ELISA technique.

Safety Observations: All AEs occurring during the treatment period, including abdominal distension, increased flatulence, borborygmus, diarrhea, abdominal cramping, and nausea, were recorded and documented.

Statistical methods

Primary and secondary outcomes were assessed among participants. Descriptive statistics are expressed as means (SD) for continuous variables or percentages for categorical variables. Normality of the data was assessed by the Shapiro-Wilk test. Differences in demographic characteristics and baseline clinical characteristics between groups were analyzed by one-way analysis of variance (ANOVA) for continuous variables and the Pearson chi-square test for categorical variables. For changes in continuous outcomes from baseline to follow-up period, analysis of covariance (ANCOVA) was used for assessment. Differences in pairwise comparisons between groups were analyzed using independent samples t-tests, and differences in pairwise comparisons within groups were analyzed using paired samples t-tests. Statistical significance was defined as $P < 0.05$.

Results

Research patients

A total of 142 patients were recruited into the study, of which 138 met the study criteria (**Figure 1**). These 138 patients were randomly assigned to 46 patients in each group. Of the 138 patients, 134 (97.10%) completed the trial. One patient in the control group withdrew from the study due to intestinal obstruction (judged by the investigators as a serious adverse event related to the underlying disease), two patients in the monotherapy group (one withdrew consent and the other for other reasons) withdrew from the trial, and one patient in the combination group (unable to contacted for follow-up) withdrew from the trial.

Baseline characteristics

The baseline characteristics of the three groups of patients were evaluated, and the results are presented in **Table 1**. The demographic and clinical profiles of the three groups were comparable, with no significant differences between them ($P > 0.05$). This included smoking and alcohol consumption ($P > 0.05$).

Clinical efficacy

Upon completion of the 56-day treatment period, the combination group achieved an overall

Table 1. Baseline demographics and clinical characteristics of the patients [Mean ± SD or n (%)]

	Control group (n=45)	Monotherapy group (n=44)	Combination group (n=45)	F/χ^2	*P* value
Age (years)	39.64 ± 14.79	40.25 ± 14.38	39.91 ± 15.11	0.010	0.981
Female allocation	21 (46.67)	18 (40.91)	23 (51.11)	0.936	0.626
Height (m)	1.63 ± 0.05	1.61 ± 0.07	1.62 ± 0.06	0.393	0.652
Weight (kg)	63.34 ± 8.62	63.13 ± 8.79	63.48 ± 7.90	0.020	0.980
BMI (kg/m^2)	24.10 ± 3.92	24.31 ± 3.92	24.40 ± 3.48	0.076	0.927
Duration of IBS (month)	9.04 ± 3.22	8.80 ± 3.51	9.24 ± 2.87	0.199	0.804
Education (year)	13.87 ± 1.59	14.51 ± 1.43	14.24 ± 1.54	2.163	0.119
Systolic BP (mmHg)	120.24 ± 7.40	119.27 ± 8.06	119.87 ± 8.25	0.170	0.844
Diastolic BP (mmHg)	78.70 ± 4.94	79.11 ± 5.04	79.53 ± 4.87	0.327	0.721
Alcohol consumption				0.960	0.916
None, n (%)	9 (20.00)	11 (25.00)	11 (24.44)		
Occasions, n (%)	26 (57.78)	24 (54.55)	27 (60.00)		
frequency, n (%)	10 (22.22)	9 (20.45)	7 (15.56)		
Smoking consumption				2.703	0.609
None, n (%)	32 (71.11)	34 (77.27)	35 (77.78)		
Occasions, n (%)	9 (20.00)	4 (9.09)	6 (13.33)		
frequency, n (%)	4 (8.89)	6 (13.64)	4 (8.89)		

Table 2. Clinical effect, n (%)

	n	cure	Significant effect	effective	In vain	Total effective rate
Control group	45	9 (20.00)	9 (20.00)	16 (35.56)	11 (24.44)	34 (75.56)
Monotherapy group	44	13 (29.55)	16 (36.36)	12 (27.27)	3 (6.82)	41 (93.18)
Combination group	45	18 (40.00)	27 (60.00)	10 (22.22)	0 (0)	45 (100.00)
χ^2				25.927		
P				< 0.001		

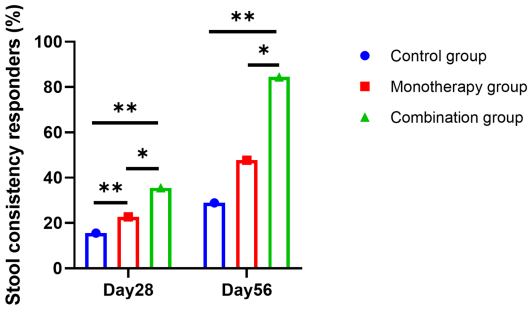

Figure 2. Consistent stool response.

clinical effectiveness rate of 100.00%, which was markedly superior to that of the monotherapy group (93.18%) and the control group (75.56%) ($P < 0.05$). See **Table 2**.

BSS

Figure 2 shows the percentage of participants who were fecal consistency responders based on a 50% or greater reduction from baseline in the number of days with at least one type 1-2 stool per week. On day 56, the proportion of fecal consistency responders was 47.73% in the monotherapy group and 84.44% in the combination group, compared to 28.89% in the control group. Additionally, the combination group demonstrated a significantly greater number of responders compared to the monotherapy group ($P < 0.05$).

IBS-QoL/PSS

On day 0, there were no significant differences in IBS-QoL or PSS scores among the three patient groups ($P > 0.05$). By Days 28 and 56, IBS-QoL scores had increased and PSS scores had decreased in all three groups, with the most pronounced trend observed in the combination group ($P < 0.05$). See **Figure 3**.

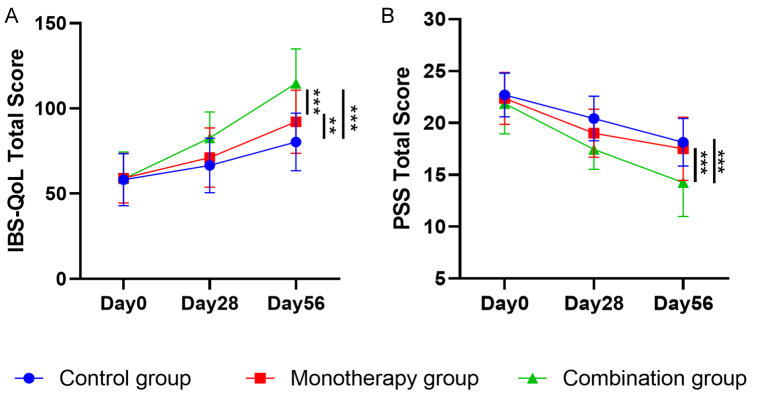

Figure 3. A. IBS-QoL total score; B. PSS total score. IBS-QoL, Irritable Bowel Syndrome Quality of Life; PSS, Perceived Stress Scale. *P < 0.05, **P < 0.05, ***P < 0.001.

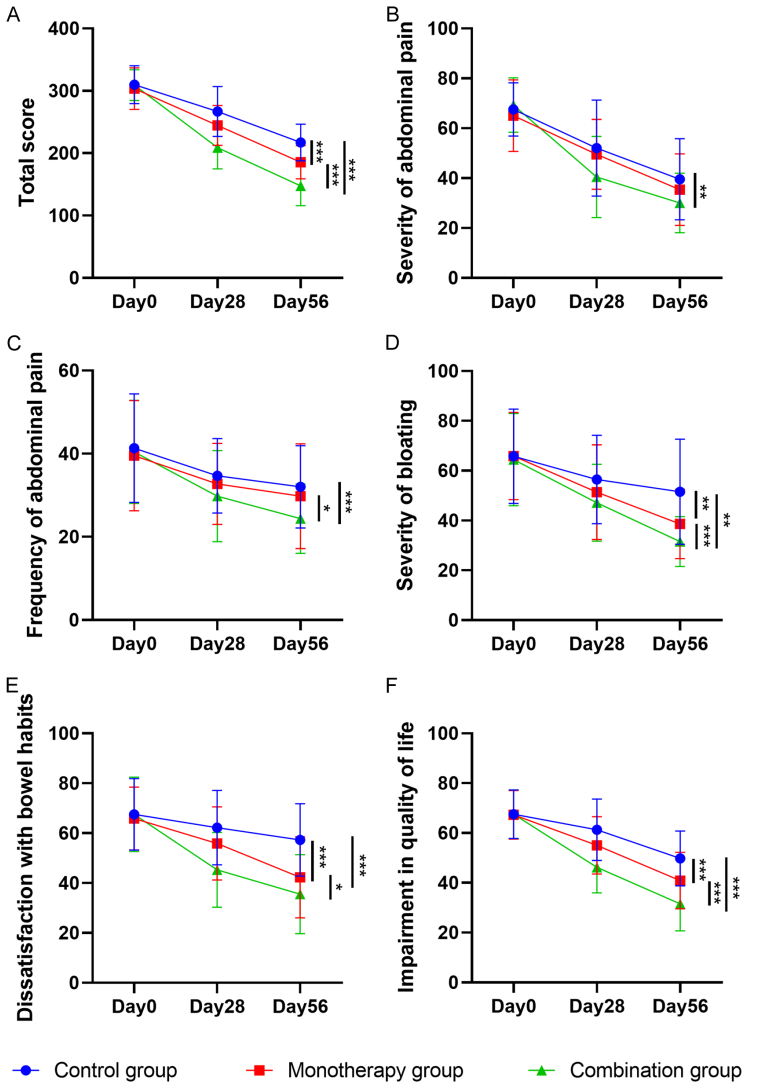

Figure 4. IBS-SSS symptom severity total and domain specific scores over the intervention period. A. Total scores; B. Severity of abdominal pain; C. Frequency of abdominal pain; D. Severity of bloating; E. Dissatisfaction with bowel habits; F. Impairment in quality of life. *P < 0.05, **P < 0.01, ***P < 0.001.

IBS-SSS

On day 0, no significant differences were observed in the total IBS-SSS scores or scores across individual domains among the three patient groups (P < 0.05). During the treatment period, total IBS-SSS scores and scores across all domains decreased in all three groups, with the combination group exhibiting significantly lower scores than both the control group and the monotherapy group (P < 0.05). See **Figure 4**.

Intestinal flora

On day 0, there were no significant differences in the detection of intestinal megacolon, Fibrinobacteriaceae, Campylobacter, and Rumenobacteriaceae among the three groups (P > 0.05). During the treatment period, the levels of Trichosporonaceae and Ruminococcaceae decreased, while Fibrobacteriaceae and Campylobacteriaceae increased, with these changes being more evident in the combination group. By day 56, the differences in these four bacterial families between the monotherapy group and the combination group were significant compared to baseline (P < 0.05). See **Figure 5**.

Gastrointestinal hormones

Before treatment, there were no statistically significant differences in MTL and VIP levels among the three groups (P > 0.05). By day 56, MTL levels increased and VIP levels decreased in all three groups,

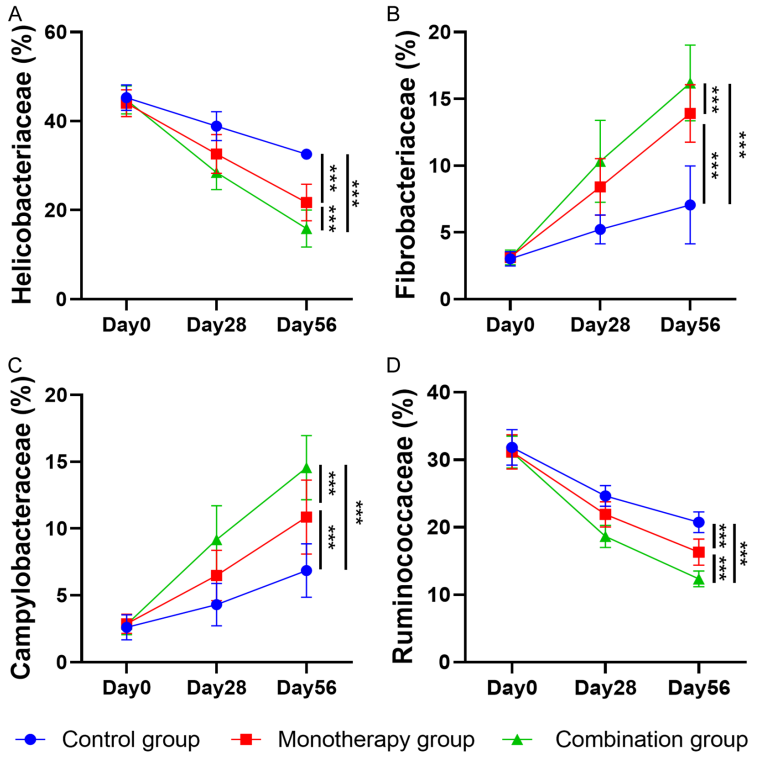

Figure 5. Changes in gut microbiota during the intervention period. A. Helicobacteriaceae; B. Fibrobacteriaceae; C. Campylobacteriaceae; D. Rumatobacteriaceae. *P < 0.05, **P < 0.01, ***P < 0.001.

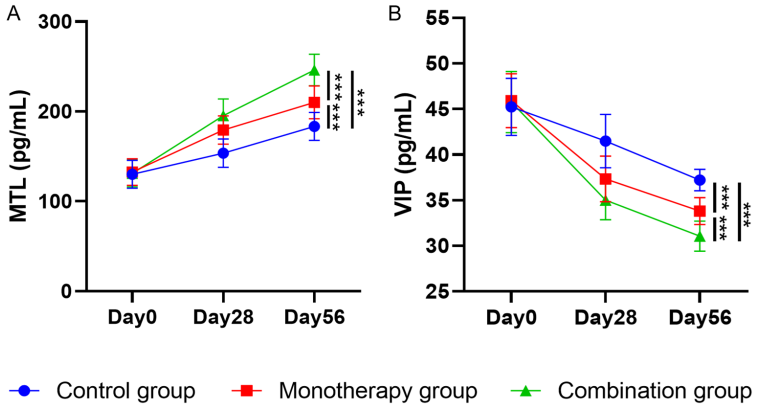

Figure 6. Gastrointestinal hormone levels over the intervention period. A. MTL; B. VIP. MTL, Motilin; VIP, Vasoactive Intestinal Peptide. *P < 0.05, **P < 0.01, ***P < 0.001.

with the most pronounced changes observed in the combination group (P < 0.05). See **Figure 6**.

Safety observations

There was no significant difference in the incidence of AEs among the three groups (P > 0.05). See **Table 3**.

Discussion

Lactobacillus rhamnosus is a widely used probiotic often employed as a supplement to promote gut health [17]. It has the ability to regulate intestinal flora, boost the immune system, and relieve allergy symptoms. It has shown significant clinical efficacy in the treatment of IBS, inflammatory bowel disease (IBD), and antibiotic-associated diarrhea [18]. Lactulose is an osmotic laxative that is broken down into lactic acid and acetic acid in the colon after oral intake. It assists in the regulation of intestinal flora disorders by lowering intestinal pH and promoting peristalsis in the colon [19]. Lactulose also fosters the growth of probiotics such as *Lactobacillus rhamnosus* and *Bifidobacterium bifidum*, further optimizing the intestinal microenvironment [20]. In this study, the combinatied treatment group achieved a clinical effectiveness rate of 100%, which was markedly superior to the rates observed in the control and monotherapy groups. Furthermore, by analyzing stool consistency response, there was a significant reduction in the number of type 1 or type 2 stool forms (hard or lumpy stools) in the combination therapy group. This suggests that the combination therapy not only improved the frequency of bowel movements but also optimized stool texture and reduced constipation symptoms. Hyeji Kwon et al. [21] also found that *Lactobacillus rhamnosus* showed significant improvement in both irritative bowel movements and constipation-induced discomfort over an 8-week treatment period. Ma et al. [22] found that in patients with chronic functional constipation, lactulose was able to increase the abundance of probiotics and optimize the intestinal microenvironment,

Table 3. Safety observations, n (%)

Group	n	Abdominal distention	Diarrhea	Bowel sounds	Nausea and vomiting	dizziness and headache	Overall Incidence
Control group	45	2 (4.44)	0 (0.00)	1 (2.22)	1 (2.22)	2 (4.44)	6 (13.33)
Monotherapy group	44	2 (4.55)	1 (2.27)	0 (0.00)	0 (0.00)	1 (2.27)	4 (9.09)
Combination group	45	1 (2.22)	1 (2.22)	0 (0.00)	0 (0.00)	1 (2.22)	3 (6.67)
χ^2					1.169		
P					0.557		

thereby relieving constipation. These findings further support the potential benefits of *Lactobacillus rhamnosus* and lactulose in the management of IBS-C.

IBS is closely associated with a range of factors, with psychological factors being particularly important in exacerbating symptoms and reducing quality of life [23]. Numerous studies have shown that IBS patients are often accompanied by mood disorders such as anxiety and depression. These psychological factors not only exacerbate the clinical symptoms of IBS but also significantly reduce patients' quality of life [24]. A study by Farndale et al. [25] further revealed the long-term effects of IBS on the daily lives of patients, noting significant changes in mood and a decrease in quality of life for those with IBS. In addition to distressing physical symptoms, patients with IBS face mood swings and limitations in social functioning, which collectively affect the patient's overall health. Further research has shown that there is a significant interaction between psychological factors and the symptoms of IBS: anxiety and depressive symptoms can exacerbate gastrointestinal symptoms, and in turn, persistent gastrointestinal distress may exacerbate psychological burdens [26]. This dual physical and psychological burden makes the symptoms and quality of life for people with IBS often more complex and difficult to manage. In this study, the effect of the combination treatment group was significantly better than that of the monotherapy group and the control group. The post-treatment IBS-QoL total scores and PSS total scores were significantly more improved in the combination treatment group ($P < 0.05$), indicating that this treatment regimen was not only effective in improving the physical symptoms of IBS-C patients but also significantly improved their emotional state and quality of life. Additionally, the IBS-SSS scoring system is widely used to assess the severity of symptoms in patients with IBS. The results showed that the combination treatment group demonstrated significant improvement in both the total IBS-SSS score and the specific scores of each dimension. Particularly in the case of abdominal pain, bloating, and bowel regularity, the combination treatment regimen effectively alleviated these key symptoms that plagued the patients. With the improvement of these symptoms, the patients' daily lives became more comfortable, and their quality of life was significantly improved. This also provides a new therapeutic idea for the comprehensive management of IBS-C.

The gut microbiota are crucial for maintaining normal gastrointestinal motility [27]. Extensive research indicates that it is involved in the pathophysiology of IBS, with both qualitative and quantitative alterations in the gut microbiota observed in patients [28]. Dysbiosis of the intestinal flora may trigger IBS through several mechanisms. First, the gut microbiota plays a significant regulatory role in the intestinal immune system. Under normal conditions, gut microbes help maintain the stability of the intestinal immune system by interacting with intestinal epithelial cells and immune cells. However, when the intestinal flora is dysbiotic, this immunoregulatory function may be disrupted, leading to abnormal activation of the immune system, which in turn triggers an intestinal inflammatory response and symptoms such as abdominal pain, diarrhea, or constipation. Secondly, gut microbes influence the neuromuscular function of the intestinal wall through interactions with the intestinal epithelium and regulate intestinal peristalsis and digestion through metabolites (e.g., short-chain fatty acids) [29]. Dysbiosis of the intestinal flora may result in decreased or altered secretion of these metabolites, which may affect normal intestinal motility and trigger symptoms such as constipation or diarrhea [30, 31]. In this

study, we found that the treatment regimen combining *Lactobacillus rhamnosus* and lactulose was able to regulate the composition of the intestinal flora more effectively. Specifically, it reduced the proportion of potentially harmful bacteria, such as Trichosporonaceae and Ruminococcaceae, while increasing the proportion of beneficial bacteria, such as Fibrobacteraceae and Campylobacteraceae ($P < 0.05$). This suggests that combination therapy helps to restore the balance of intestinal microecology by optimizing the structure of the intestinal flora. Previous studies have also found that Lactobacillus rhamnosus was able to increase butyric acid levels while decreasing propionic acid levels [32]. Short-chain fatty acids, which are products of dietary fiber fermentation by intestinal microbes, have anti-inflammatory effects and modulate intestinal barrier function. *Lactobacillus rhamnosus* may further improve immune and motility functions in the gut by modulating short-chain fatty acid levels [33]. The mechanism of action of lactulose is complementary to that of *Lactobacillus rhamnosus*. In IBS-C patients, the imbalance of intestinal flora is usually accompanied by constipation symptoms, and lactulose can increase the water content in the colon, improve fecal softening, and promote intestinal peristalsis, thus relieving constipation symptoms [34]. Therefore, the combination *of Lactobacillus rhamnosus* and lactulose not only improves the intestinal microecology by regulating the structure of intestinal flora and metabolites but also enhances intestinal peristalsis through a synergistic effect, which relieves constipation symptoms in IBS-C patients more effectively.

It is now believed that visceral hypersensitivity is the key pathophysiologic mechanism of IBS-C, and dysfunction of the brain-gut axis is an important cause of visceral hypersensitivity [35]. The brain-gut axis is a complex network connecting the gastrointestinal tract with the central nervous system, in which brain-gut peptides play an important regulatory role as neurotransmitters [36]. These peptides are widely distributed in the central nervous system, gastrointestinal tract, and immune organs, and they can regulate gastrointestinal motor and sensory functions through neural, endocrine, and immune pathways. They are closely related to symptoms of visceral hypersensitivity, such as abdominal pain, abdominal discomfort, and defecation abnormalities [37]. MTL and VIP are distributed in the enteric nervous system. MTL is a key hormone that regulates gastrointestinal motility by activating neurons and muscle cells, thereby maintaining normal digestive function. However, IBS-C patients have reduced levels of MTL, leading to slowed gastrointestinal motility, which in turn exacerbates constipation symptoms. Meanwhile, VIP, as an inhibitory neurotransmitter, can relax the smooth muscle of the gastrointestinal tract, inhibit gastrointestinal peristalsis, and promote gastric mucosal gland secretion [38]. Elevated levels of VIP in IBS-C patients further inhibit intestinal peristalsis, thereby triggering constipation. The results of the present study showed that the combination treatment could significantly increase MTL levels while decreasing VIP levels. This modulating effect helps to restore the normal peristaltic function of the gastrointestinal tract, thus relieving constipation symptoms. Furthermore, no statistically significant differences in adverse event rates were observed among the three patient groups, further confirming the favorable safety profile and clinical feasibility of the combination therapy.

This study had several limitations. First, the relatively small sample size and single-center design may have limited the generalizability of the findings. Second, although the 56-day intervention period was sufficient to assess short-term efficacy, it did not allow for evaluation of the long-term sustainability of the therapeutic effects. Additionally, while the study focused on changes in gut microbiota structure and gastrointestinal hormones, the detection of key metabolites such as short-chain fatty acids was insufficient. Finally, although improvements in psychological status were observed, the specific mechanisms underlying brain-gut axis interactions were not thoroughly investigated. Future studies should adopt a multicenter design to increase sample size, implement longer intervention and follow-up periods, and integrate metabolomics and neuroimaging techniques to further elucidate the mechanisms of the combination therapy.

In conclusion, the therapeutic regimen of *Lactobacillus rhamnosus* combined with lactulose showed significant clinical advantages in the management of IBS-C. The combination therapy significantly relieved patients' consti-

pation symptoms and improved their quality of life by modulating gastrointestinal hormone levels and optimizing the structure of the intestinal flora.

Disclosure of conflict of interest

None.

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