

# Clinical observation of probiotics combined with mesalazine in the treatment of ulcerative colitis

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**Abstract:** To analyze the clinical efficacy of probiotics combined with mesalazine in the treatment of ulcerative colitis. 112 patients with ulcerative colitis admitted to the Department of Anorectal Surgery, Affiliated Hospital of Qingdao University from December 2016 to October 2018 were collected. The cases were randomly divided into control group (56 cases; mesalazine treatment) and study group (56 cases; Probiotics combined with mesalazine treatment). After 2 months, the inflammatory factor levels, treatment efficiency and adverse reactions were analyzed. The serum IL-6, TNF- $\alpha$ , and IFN- $\gamma$  levels of the study group was superior to the control group ( $P < 0.05$ ). The total effective rate of treatment in the study group was 92.86%, which was significantly higher than that in the control group 76.79% ( $P < 0.05$ ). The incidence of adverse reactions in the study group was 7.14%, which was significantly lower than that of the control group 21.43% ( $P < 0.05$ ). Combined Probiotics and Mesalazine maintain the treatment of Ulcerative colitis with remarkable curative effect and less adverse reactions.

**Keywords:** Probiotics; Mesalazine; Ulcerative colitis; Clinical efficacy

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## 1. Introduction

Inflammatory bowel disease (IBD) is a chronic non-specific intestinal inflammatory disease, mainly including Ulcerative colitis (UC) and Crohn's disease (CD). It is clinically characterized by abdominal pain, diarrhea, mucous pus and bloody stools. Sense is the main performance [1,2]. The etiology and pathogenesis of IBD are still unclear. The existing findings suggest that it is caused by the interaction of genetic, immunological, environmental factors and intestinal infection[3]. Therefore, the research and treatment methods are mostly based on its pathogenic mechanism, mainly through the use of anti-inflammatory drugs, such as aminosalicylic drugs, corticosteroids, immunosuppressive agents, biological agents, etc.[2]. Clinically, oral administration of oral salicylic acid drugs such as mesalazine can significantly improve intestinal inflammation[4], but the cost of treatment is higher, the incidence of adverse reactions is higher, and the disease is prone to recurrence. Currently, there is no drug treatment.

Intestinal flora imbalance is closely related to the occurrence and development of UC. In recent years, clinical trial studies have shown that there are different degrees of dysbacteriosis in the intestinal tract of patients with UC[5]. Regulation of intestinal microbes can be carried out by antibiotics or probiotics. The former is not suitable for chronic diseases because antibiotics have drug resistance and potential side effects[6]. There is evidence that probiotic *Escherichia coli* strains have a significant therapeutic effect on ulcerative colitis, and the

combination of mesalazine and probiotics may have synergistic or additive therapeutic effects on ulcerative colitis[7]. Therefore, this study aimed to observe the clinical efficacy and feasibility of probiotics combined with mesalazine in the treatment of patients with ulcerative colitis.

## 2. Information and methods

### 2.1. General Information

112 patients with UC admitted to the Department of Anorectal Surgery, Affiliated Hospital of Qingdao University from December 2016 to October 2018 were randomly divided into study group and control group. The study group (56 cases): 31/25 males and females, aged 18 to 64 years, mean age ( $41.2 \pm 9.4$ ) years, duration of disease 1 to 9 years, mean disease duration ( $5.3 \pm 3.5$ ) years; control group (56 cases): the ratio of male to female is 30/26, age 19-66 years old, mean age ( $41.4 \pm 9.7$ ) years, duration of disease 2 to 10 years, mean disease duration ( $5.6 \pm 3.7$ ) years.

Inclusion criteria are age  $> 18$ , colonoscopy and histopathology, all patients with ulcerative colitis, UC lesions involving at least the rectum, sigmoid colon area. Stable dose of aminosalicylic acid has been administered orally for at least 4 weeks and no communication disorder.

Exclusion criteria are patients with Crohn's disease or colon diverticulitis, persons in need of emergency surgery or the combination of major diseases such as cerebral heart and kidney, oral corticosteroids or antibiotic use within two weeks of the last 4 weeks before the start of the study, overuse of probiotic

preparations within 2 weeks of entering the study; patients with acute diarrhea, dehydration, severe complications such as digestive tract hemorrhage and persons with intellectual disabilities.

There were no significant differences in gender, age, and duration of disease between the two groups ( $P>0.05$ ). The study was approved by the local ethics committee and all participants to sign an informed consent form.

## 2.2. Treatment

Control group: patient with 1.5g of mesalazine sustained-release granules (Shanghai Aifa Pharmaceutical Co, Ltd.; specification: 0.5g×10 bags; national drug standard H20143164), 3 bags/time, 3 times/d.

Study group: patients with oral mesalazine sustained-release granules (usage, dosage see control group), at the same time, oral Bifidobacterium triple live bacteria enteric-coated capsules (Beida), national medicine Zhunzi S19993065, produced in Jincheng Haisi Pharmaceutical Co., Ltd., specifications 0.21g × 24, 3/time, 3 times/d, warm boiled water.

After the two groups of patients used the three meals, the food avoid spicy foods such as spicy foods

and seafood, which are easy to induce recurrence or aggravation of Ulcerative colitis. Both groups were treated for 2 months with regular anti-inflammatory treatment.

## 2.3. Observation indicators

### 2.3.1. Mayo Disease Activity Index Score

Mayo rating was according to the references[8]. The scoring criteria are shown in table 1, the total cases were divided into symptom relief, mild activities, moderate activities and heavy activities group basis on the score <2, 3~5, 6~10 and 11~12, respectively. Disease activity index score reduced percentage = [(pre-treatment disease activity Index score-post-treatment disease activity index score)/pre-treatment disease activity index score]×100%. Effectiveness refers to the reduction of Mayo score ≥50%, ≥25%, and < 50%. Invalid refers to the reduction of Mayo score after treatment < 25%. Total efficiency = [(number of effective cases + number of valid cases)/Total number of cases] ×100%.

**Table 1. Mayo Disease Activity index scoring criteria**

Project	0	1	2	3
Stool frequency	Normal	1– 2Stools/day>normal	3– 4Stools/day>normal	>4Stools/day>normal
Rectal bleeding	None	Streaks of blood	Obvious blood	Mostly blood
Mucosal appearance	Normal	Mild friability	Moderate friability	Exudation, spontaneous
Physician rating of disease activity	Normal	Mild	Moderate	Severe

### 2.3.2. Inflammatory factor levels in two groups

Serum inflammatory factor was detected in patients with fasting vein blood before treatment and within 1 weeks after treatment. IL-6, TNF-α and IFN-γ were determined by enzyme-linked immunosorbent test, and the instrument was 2550 enzyme-linked immune tester (American Bio-rad Company).

## 2.4. Data analysis

The SPSS17.0 software was used to the data analysis.  $\chi^2$  and t test were used for the measurement data and counting data respectively.  $p<0.05$  is statistically significant.

## 3. Results

### 3.1. Mayo Disease Activity Index Score

After the treatment of 2 groups of patients, diarrhea, hemorrhage and the appearance of mucosal changes in colonoscopy were lower than before treatment, and the difference was statistically significant ( $P<0.05$ ). The study Group's Mayo Disease Activity Index score was reduced from  $7.13\pm 1.89$  to  $1.46\pm 1.19$ , the control group was reduced from  $7.30\pm 1.91$  to  $2.89\pm 1.08$ , and the difference in the decrease of 2 groups was statistically significant ( $P<0.05$ ). see Table 2.

### 3.2. Comparison of the integrated effect between two group

After treatment in the 2 groups, the total effective rate of treatment in the study group was 92.86%, which was significantly higher than that in the control group 76.79%,  $p<0.05$ , see Table 3.

**Table 2. Comparison of Mayo scores between two groups of patients before and after treatment**

Group	n	Before treatment	After treatment
Research group	56	7.13±1.89	1.46±1.19*#
Control group	56	7.30±1.91	2.89±1.08

note: \* compared with before treatment, P<0.05; # compared with the control group, P<0.05

**Table 3. Comparison of the integrated effect between two groups (n, %)**

Group	Significant effect	Effective	Invalid	Efficient
Research group (n=56)	33	19	4	92.86% (52/56)
Control group (n=56)	16	27	13	76.79% (43/56)
$\chi^2$	-	-	-	5.6173
P	-	-	-	0.0178

**Table 4. Serum IL-6, TNF- $\alpha$ , and IFN- $\gamma$  level**

Group	IL-6 (pg/ml)	TNF- $\alpha$ (ng/ml)	IFN- $\gamma$ (pg/ml)
Research group (n=56)	9.16±3.15	1.17±0.72	2.13±0.53
Control group (n=56)	15.37±5.31	2.68±1.57	5.58±1.37
T	7.5269	6.5422	17.5755
P	0.0001	0.0001	0.0001

**Table 5. Adverse Reactions (n, %)**

Group	Nausea	Anomaly	Rash	Gastrointestinal reaction	Incidence rate
Research group (n=56)	1	1	1	1	7.14% (4/56)
Control group (n=56)	4	3	2	3	21.43% (12/56)
$\chi^2$	-	-	-	-	4.6667
P	-	-	-	-	0.0308

### 3.3. Serum inflammatory factor levels

The results in Table 4 showed that serum IL-6, TNF- $\alpha$ , and IFN- $\gamma$  levels decreased after treatment in both groups, and the decrease in the study group was more significant, p<0.05 (Table 4).

### 3.4. Adverse reactions

The results in Table 5 show that the incidence of adverse reactions in the study group was significantly lower than that in the control group, p<0.05. It is speculated that probiotics combined with mesalazine can improve the quality of life of patients.

## 4. Discussion

Ulcerative colitis is a chronic non-specific inflammatory disease of the colon and rectum that is not yet well known, and the lesion is confined to the

mucosa of the large intestine and the lower mucosa. The lesions are mostly located in the sigmoid colon and rectum and can also extend to the descending colon, or even the entire colon[9]. In recent years, with the change of people's diet and living habits, the incidence rate of the disease shows a trend of increasing year by year, which has a seriously impact on the health and life persons[10]. Current studies have shown that ulcerative colitis is associated with intestinal immune disorders, the environment and intestinal flora[11]. Among them, intestinal flora imbalance, the number of probiotics (Bifidobacterium, Lactobacillus, etc.) in the gut decreased significantly, germs and other metabolites on the intestinal immune system of the normal function of the impact, resulting in epithelial tissue damage, causing inflammation[11,12]. The inflammatory response of IL-6, TNF- $\alpha$ , IFN- $\gamma$ , etc. levels will rise[13], resulting in fever in patients.

Mesalazine granules are commonly used in the treatment of UC. Mesalazine granules are a sustained

release dosage form of 5-aminosalicylic acid. They are encapsulated in an enteric coating and can be released at the end of the colon and ileum by inhibiting prostaglandin E2 (PEG2). Leukotriene B4 (LTB4) and platelet activity factor (PAF) are easy to trigger the synthesis of colonic mucosal inflammatory mediators to inhibit the development of inflammation[4,14]. It can remove free radicals in the colon, regulate the oxidation/antioxidant balance, reduce intestinal mucosal damage, and finally achieve the purpose of treating intestinal ulcers. It is one of the drugs of choice for clinical treatment of UC[15]. However, the use of mesalazine alone has a higher incidence of adverse reactions and is prone to recurrence[16]. Analysis of the reasons may be related to the dysbacteriosis of intestinal flora in UC patients. Intestinal flora imbalance can directly affect antigen stimulation, intestinal epithelial cell metabolism, mucosal immune response, aggravating the occurrence and development of UC[17,18].

With the developing of microecology, the treatment of probiotics that are harmless to the human body has gradually attracted people's attention. Studies have shown that probiotics have a good effect on the imbalance of intestinal flora and the relief of inflammatory response[11]. It can supplement the quantity of probiotics in the intestine, balance the intestinal flora, inhibit the development of pathogenic bacteria, and plays the biological role of probiotics, and protect the intestinal mucosal barrier function[19]. Due to the gradual broadening of the selection and application range of probiotics, probiotics are also used in the treatment of inflammatory bowel disease. At the same time as the therapeutic effects similar to those of anti-inflammatory drugs, no obvious adverse reactions[20]. The exact mechanism by which probiotics exert their beneficial effects is unclear, and different strains have different roles and mechanisms of action. A study found that probiotics such as non-pathogenic *Escherichia coli*, bula yeast and *Lactobacillus bacillus* were effectively in the treatment of mild to moderate active ulcerative colitis[21]. Shen and other studies[22] also believe that probiotics can induce the remission of active UC patients, in addition, probiotics similar to 5-amino acid preparation for UC patients have the effect of maintaining relief, and no toxic side effects[23].

In recent years, foreign scholars have more research on the effect of TNF- $\alpha$ , IL-17 and IL-23 on inflammatory diseases[9]. However, there is no comparative study before and after the treatment of probiotics combined with Mesalazine in UC. In this study, the clinical data of 56 cases of UC patients treated with Mesalazine treated and 56 cases with Mesalazine combined with probiotics were analyzed, and our results confirmed that the laboratory indexes were significantly improved after treatment with probiotics. In the course of this treatment, the effective rate of the patients in the study group was

significantly better than that in the control group. The levels of serum IL-6, TNF- $\alpha$  and IFN- $\gamma$  decreased significantly in the study group, and the comparison of the above indexes between the two groups was statistically significant. It is shown that probiotics play a role in improving the inflammatory performance of UC, while probiotics are cheaper and safer than other drugs, and the method of combined treatment with other drugs is worth popularizing in UC therapy[24].

At present, there are few clinical trials on the therapeutic effect of probiotics on IBD, and the sample size is small, and further large sample clinical trials are needed. In future studies, in addition to increasing the number of selected patients, we can also extend the study time, through this study shows that the United States Mesalazine combined with probiotics and standardized treatment, can improve the life and quality of patients, reduce clinical symptoms and reduce the risk of recurrence. With the in-depth study of the practical value of probiotics in the treatment of inflammatory bowel disease, it is believed that the convenient and safe and effective microecological treatment method of probiotics will be widely accepted by people.

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