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ORIGINAL RESEARCH

Effect of Intestinal Microbiota Transplantation on Intestinal Flora and Inflammatory Factor Levels in Patients with Ulcerative Colitis

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Objective: The present study was performed to evaluate the effect of intestinal microbiota transplantation (IMT) on intestinal flora and inflammatory factor levels in patients with ulcerative colitis (UC).

Methods: In this study, 94 UC patients who attended the Department of Proctology or the Department of Gastroenterology departments of Sinopharm Dongfeng General Hospital between April 2021 and April 2022 were identified as research participants and were assigned to the control or Research Groups via the random number table method, with 47 cases in each group. Interventions included oral mesalamine for patients in the control group and oral mesalamine plus IMT for those in the research group. Outcome measures included clinical efficacy, intestinal microbiota score, enteroscopy score, Sutherland index, inflammatory factor level, intestinal mucosal barrier function level, and adverse reactions.

Results: Mesalamine plus IMT was associated with significantly higher treatment efficiency (97.8%) versus mesalamine alone (80.85%) ($P<0.05$). Mesalamine plus IMT provided a better intestinal microbiota balance and milder disease symptoms versus mesalamine, as evidenced by the significantly lower intestinal microbiota scores, colonoscopy scores, and Sutherland index ($P<0.05$). In post-treatment, patients with IMT exhibited more mitigated inflammatory responses than those without, as shown by the higher levels of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-17 (IL-17), and interleukin-23 (IL-23) ($P<0.05$). Significantly lower D-lactate and serum diamine oxidase (DAO) levels were observed after IMT intervention than those with mesalamine alone ($P<0.05$). IMT features no significant increase in adverse effects than the control group ($P>0.05$).

Conclusion: IMT efficiently ameliorates the intestinal microbiota conditions of UC patients, mitigates inflammatory responses in the body, and facilitates the restoration of intestinal mucosal barrier function with no significant increase in adverse effects.

Keywords: intestinal microbiota transplantation, ulcerative colitis, intestinal microbiota, inflammatory factors

Introduction

Ulcerative colitis is a chronic, nonspecific inflammatory disease of the colon and rectum whose etiology is not well understood, and lesions are confined to the mucosa and submucosa of the large intestine.[1] Lesions are mostly located in the sigmoid colon and rectum, but can also extend to the descending colon or even the entire colon. The course of the disease is long and often recurrent.[2] The common clinical symptoms of UC include nausea and vomiting, diarrhea, abdominal pain, bloody stools, and weight loss, characterized by long disease duration, intractability, and recurrent episodes.[3] The pathogenesis and causes of UC are clinically elusive and have been reported to be linked to environmental and genetic factors or dysbiosis of intestinal flora.[4] Gut bacteria play a key role in initiating and maintaining inflammatory processes in intestinal tissues in patients with UC by providing antigens or other stimulating factors that trigger immune cell activation.[5] Studies have shown that changes in the

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composition of the gut microbiota and a decrease in gut microbial species diversity in IBD patients are associated with the pathogenesis of UC compared to healthy controls.[6]

Antibiotics, corticosteroids, and immunosuppressants are commonly used in UC. Mild patients can be treated with drugs such as mesalamine or sulfasalazine, and if it is moderate to severe, it needs to be treated with glucocorticoids, and more severe it needs to be controlled with biological agents.[7] However, inconsistency exists in symptom mitigation among patients, and the side effects and drug resistance contribute substantially to the poor long-term medication compliance of patients.[8] Thus, there exists an urgent need to explore novel treatment modalities to improve patient prognosis. Previous research identified tremendous variations in the distribution and species of intestinal flora in patients with active UC compared with the healthy population.[9] In contrast to the previous probiotic supplementation and multiple probiotic complexes, intestinal microbiota transplantation (IMT) provides richer and more physiologically demanding flora and has been clinically employed in the management of constipation, irritable bowel syndrome, and other gastrointestinal diseases.[10]

In this study, we aimed to explore the clinical effect of IMT on intestinal flora and inflammatory factor levels in UC patients.

Materials and Methods

Participants

This study identified 94 UC patients who attended the Department of Proctology or the Department of Gastroenterology in Sinopharm Dongfeng General Hospital between April 2021 and April 2022 as research participants and assigned them to either a control group or a research group via random method, with 47 cases in each group. Participants were randomly and equally allocated into two groups using a randomization calculator (http://www.randomization.com). The study was done in accordance with Good Clinical Practice and the ethical principles originating in the Declaration of Helsinki. The protocol and informed consent document were approved by the ethics committee of Sinopharm Dongfeng General Hospital for each clinical site. Ethics No.: NU-Y20210201.

Inclusion and Exclusion Criteria

Inclusion criteria: 1) Diagnosed with UC, with the Mayo score 3 to 10; 2) the degree of ulcerative colitis did not exceed the moderate standard; 3) the patients had clinical symptoms such as abdominal pain, diarrhea, blood in stool, and vomiting; 4) the patients did not receive systematic therapeutic interventions before participating in this study; 5) the patients and their families voluntarily participated in this study and signed the relevant informed consent forms.

Exclusion criteria: 1) patients with contraindications or allergic reactions to the treatment modalities and drugs in this study; 2) systemic diseases; 3) concomitant serious infectious diseases; 4) serious organ diseases; 5) non-ulcerative colitis; 6) ulcerative colitis that has exceeded the moderate standard; 7) neoplastic diseases; 8) patients who were unable to cooperate completely with this study.

Treatment Methods

1. Patients in the two groups received four mesalamine enteric soluble tablets (Sunflower Pharmaceutical Group Jiamusi Luling Pharmaceutical Co., Ltd., State Pharmacopoeia H19980148) orally, thrice daily. The treatment duration was 30d.
2. Patients in the research group additionally received IMT. ①Donor selection: Adults under 30 years old from a standard fecal bacteria bank, with a healthy lifestyle, good dietary habits, no bad habits such as smoking and drinking, no chronic diseases, no infectious diseases, no chronic diarrhea, constipation, irritable bowel disease, and no history of antibiotic or probiotic and other drug supplements use in the past 3 months were selected. ②Preparation of flora: Fecal bacteria were prepared by the manual method: 200 g of donor stool was collected early in the morning, and 50 g of stool was dissolved in 250 mL of saline, stirred, and filtered through filter sieves of 2-, 1-, 0.5- and 0.25-mm diameter. The supernatant was removed after centrifugation, and the precipitate was resuspended with saline and stored in a −80 °C

refrigerator. ③Fecal bacteria transplantation. The frozen bacterial solution was thawed and rewarmed in a 37 °C water bath, 50 g of stool in 250 mL of saline. Transscopic intestinal implantation is adopted. The IMT was performed once a week, with a treatment duration of 30 d. During the treatment, the in-hospital medical staff provided dietary and lifestyle guidance to the patients.

Outcome Measures

1. Clinical efficacy: the treatment efficacy of patients was assessed as per the Consensus Opinion on the Diagnosis and Treatment of Inflammatory Bowel Disease. Cured: the patients' clinical symptoms disappeared, and colonoscopy showed a normal intestinal mucosa; Markedly effective: the patients' clinical symptoms were alleviated significantly, and colonoscopy showed significantly relieved inflammation of intestinal mucosa; Effective: the patients' clinical symptoms were alleviated, and colonoscopy showed relieved inflammation of intestinal mucosa; Ineffective: No significant changes were seen in patients' clinical symptoms and colonoscopy results.
2. Intestinal microflora score:[11] Before and after treatment, the intestinal microflora score was used to assess the intestinal flora of the patients. The scale is scored out of 5. The higher the score of the patient, the more serious the dysbiosis of the intestinal flora.
3. Enteroscopy score:[12] Before and after treatment, patients' intestinal mucosal conditions were assessed with a colonoscopy score out of 4. The higher the score of the patient, the more serious the intestinal mucosal symptoms.
4. Sutherland index:[13] Before and after treatment, the Sutherland index was used to assess the disease activity of patients in terms of intestinal mucosal status, rectal bleeding and diarrhea frequency. The scale was scored out of 12 points, and the higher the score of the patient, the more serious the disease symptoms.
5. Levels of inflammatory factors: Before and after treatment, 5 mL of morning fasting elbow venous blood was collected from patients and routinely centrifuged to isolate the serum. The serum concentrations of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-17 (IL-17), and interleukin-23 (IL-23) were measured by enzyme-linked immunosorbent assay (ELISA).
6. Intestinal mucosal barrier function level: Before and after treatment, 5 mL of morning fasting elbow venous blood was collected from patients and centrifuged to obtain the serum. The colorimetric method was used to determine the level of D-lactate in the patient, and the ELISA method was used to determine the level of serum diamine oxidase (DAO).
7. Adverse events: The adverse events included in this study included abdominal distension and abdominal pain, fever, nausea and vomiting, and abnormal liver function.

Statistical Analysis

The SPSS 23.0 software package was used to organize and analyze the data in this study, and GraphPad Prism 8 was used to visualize the data into corresponding graphics. Measurement data were expressed as mean±standard deviation ($\bar{x} \pm s$) and examined using the *t*-test. Count data were expressed as n(%) and tested using the chi-square test. $P < 0.05$ indicates that the difference is statistically significant.

Results

Baseline Clinical Profiles

In the control group, there were 29 males and 18 females, aged 19–72 (33.82±10.35) years, with a disease duration of 4–19 (12.35±3.87) months; there were 13 cases of mild disease and 34 cases of moderate disease, 3 cases of proctitis, 32 cases of left hemicolitis and 12 cases of total colitis. In the research group, there were 27 males and 20 females, aged 18–74 (34.07±10.28) years, with a disease duration of 5–21 (12.52±3.71) months; there were 15 cases of mild disease and 32 cases of moderate disease, 4 cases of proctitis, 30 cases of left hemicolitis and 13 cases of total colitis. The baseline clinical profiles between the two groups were comparable (P>0.05) (Table 1).

Table 1 Baseline Clinical Profiles

	Control Group (n=47)	Research Group (n=47)	t/χ^2	P
Gender (Male/Female)	29/18	27/20	0.176	0.674
Age (years)	33.82±10.35	34.07±10.28	0.117	0.906
Disease duration (month)	12.35±3.87	12.52±3.71	0.217	0.828
Disease degree			0.203	0.651
Mild	13	15		
Moderate	34	32		
Disease lesion			0.247	0.884
Proctitis	3	4		
Left hemicolitis	32	30		
Total colitis	12	13		

Clinical Efficacy

The total treatment efficiency of the control group was 80.85% (38/47), including 7 cases of cured, 12 cases of markedly effective, 19 cases of effective, and 9 cases of ineffective. The total treatment efficiency of the Research group was 97.87% (46/47), including 13 cases of cured, 16 cases of markedly effective, 18 cases of effective, and 1 case of ineffective. Mesalamine plus IMT was associated with significantly higher treatment efficiency (97.8%) versus mesalamine alone (80.85%) ($P<0.05$) (Table 2).

Intestinal Flora Score, Enteroscopy Score, and Sutherland Index

In the control group, the intestinal flora scores before and after treatment were (3.22±0.38, 2.48±0.57), the colonoscopy scores were (3.14±0.62, 1.85±0.43), and the Sutherland index was (8.06±1.82, 4.49±0.65). The intestinal flora scores before and after treatment in the Research group were (3.19±0.35, 1.72±0.38), the enteroscopy scores were (3.19±0.57, 1.17±0.35), and the Sutherland index was (7.97±1.84, 3.34±0.42). Mesalamine plus IMT provided a better intestinal microbiota balance and milder disease symptoms versus mesalamine, as evinced by the significantly lower intestinal microbiota scores, colonoscopy scores, and Sutherland index ($P<0.05$) (Figure 1).

Inflammatory Factor Levels

In the control group, the levels of TNF-α before and after treatment were (3.84±0.83, 3.38±0.69), IL-1β were (13.28±3.45, 7.46±1.27), IL-17 were (466.35±56.47, 343.25±64.27), and IL-23 were (855.64±103.41, 436.17 ±67.64). In the Research Group, the levels of TNF-α before and after treatment were (3.85±0.84, 2.81±0.57), IL-1β were (12.98±3.69, 3.44±0.75), IL-17 were (470.54±60.58, 213.28±67.42), and IL-23 were (856.32±101.29,

Table 2 Clinical Efficacy [n (%)]

Group	Control Group	Research Group	χ^2	P
n	47	47		
Cured	7	13		
Markedly effective	12	16		
Effective	19	18		
Ineffective	9	1		
Total efficacy (%)	80.85%	97.87%	7.161	0.007

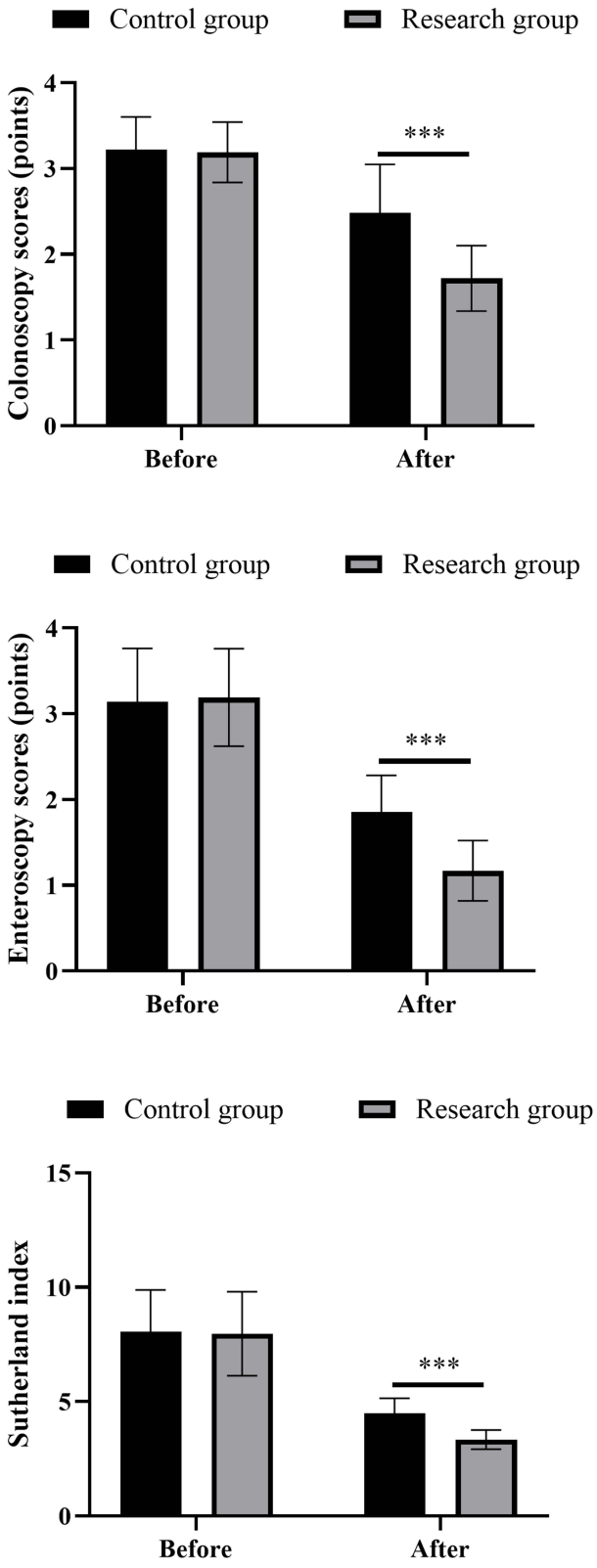

Figure 1 Intestinal flora score, enteroscopy score, Sutherland index.
Note: ***Indicates P<0.001.

331.47±45.39). In post-treatment, patients with IMT exhibited more mitigated inflammatory responses than those without, as shown by the higher concentrations of TNF-α, IL-1β, IL-17, and IL-23 (P<0.05) (Figure 2).

Intestinal Mucosal Barrier Function

In the control group, the levels of D-lactate before and after treatment were (16.57±4.23, 12.89±3.27) and DAO were (4.99±1.34, 4.01±0.98). In the research group, the levels of D-lactate before and after treatment were (16.84±4.41, 8.72 ±3.68) and DAO were (5.04±1.41, 2.36±0.29). Significantly lower D-lactate and serum DAO levels were observed after IMT intervention than those with mesalamine alone (P<0.05) (Figure 3).

Adverse Events

The incidence of adverse events in the control group was 8.51% (4/47), including 2 cases of abdominal distension and abdominal pain, 1 case of fever, and 1 case of nausea and vomiting. The incidence of adverse events in the Research Group was 12.77% (6/47), including 2 cases of abdominal distension and abdominal pain, 1 case of fever, 2 cases of nausea and vomiting, and 1 case of abnormal liver function. IMT features no significant increase in adverse effects than the control group (P>0.05) (Table 3).

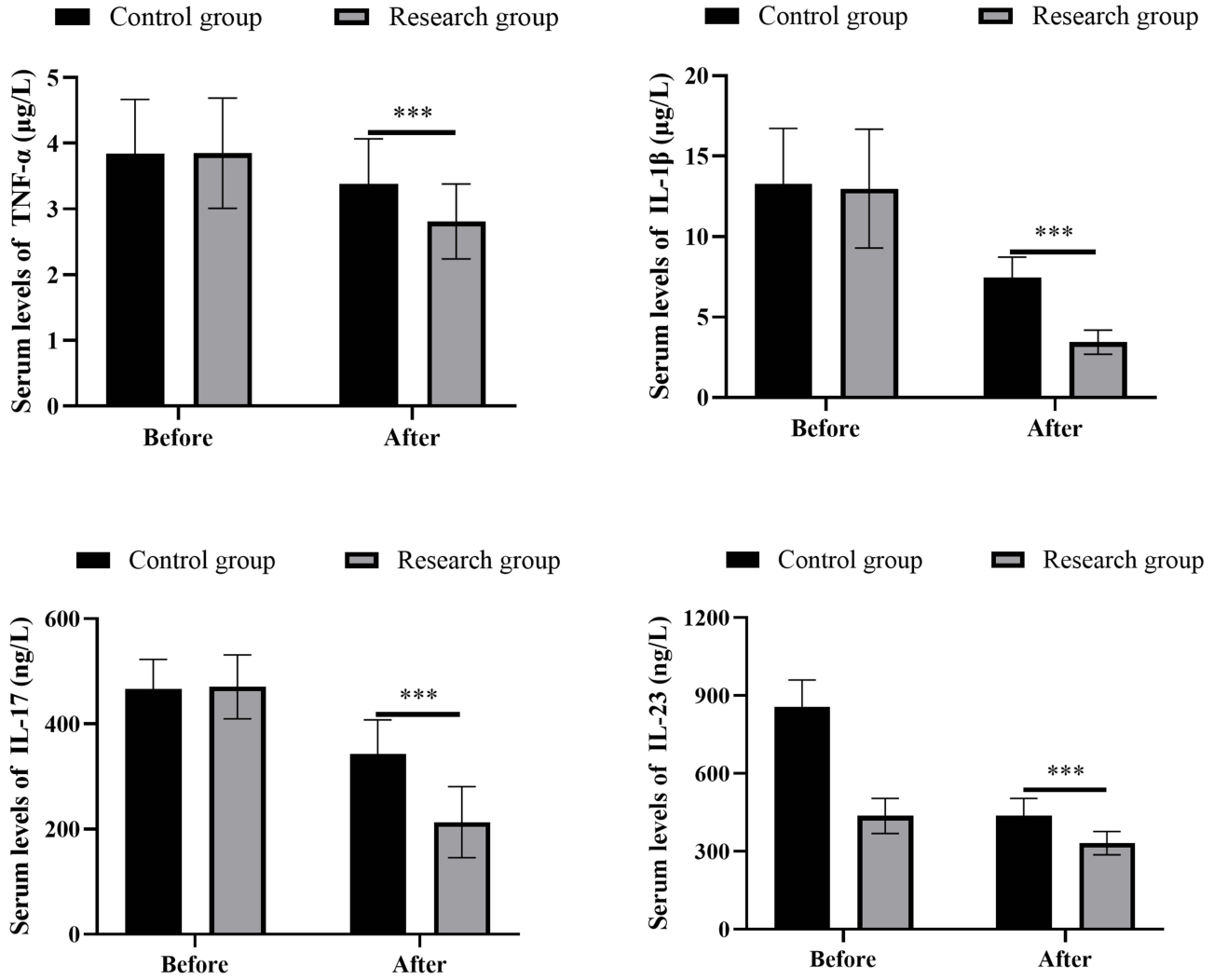

Figure 2 Inflammatory factor levels.
Note: ***Indicates P<0.001.

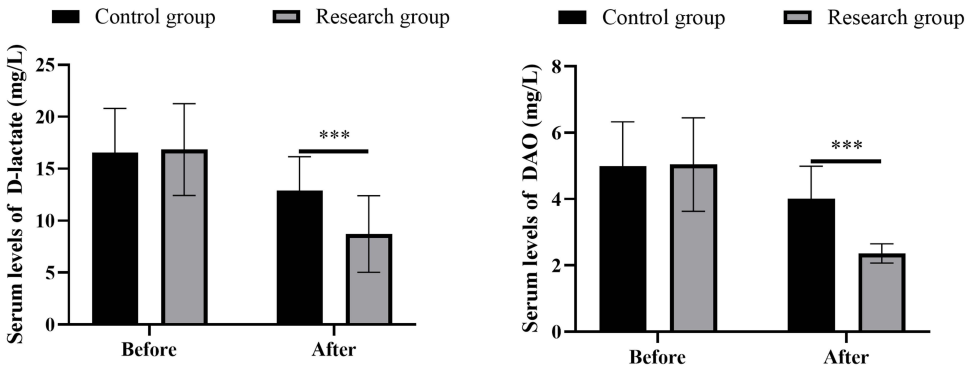

Figure 3 Intestinal mucosal barrier function.
Note: ***Indicates P<0.001.

Discussion

Relevant research has shown that abnormalities in the intestinal microbiota may increase intestinal permeability, which reduces the thickness of the protective mucus layer and exacerbates the risk of pathogen invasion.[14] The mucus layer of the human intestinal wall is produced by cupped cells, which act as both a mechanical and a chemical protective barrier.[15] It was found that cup cells in patients with chronic inflammatory intestinal diseases are highly susceptible to damage, which affects the integrity and barrier function of the intestinal mucosa, leading to bacterial translocation and aggregation of T cells and inflammatory factor cells.[16] It interferes with the stability of the intestinal microbiota and further aggravates tissue damage. In recent years, a large number of studies have confirmed that the intestinal hyperinflammatory response caused by imbalance between gut microbiota and mucosal immunity is closely related to UC.[17] In UC patients, the number of microorganisms in the gut and the diversity and stability of intestinal bacteria were impaired, the number of proprietary Firmicutes decreased, and the number of Bacteroides and anaerobic microorganisms increased.[18] Therefore, improvement of intestinal flora in UC patients is a new approach to interrupt this vicious cycle and enhance the overall patient outcome. Probiotics are a kind of live microorganisms beneficial to the host, which can repair the damaged mucosal barrier to provide a good growth environment for beneficial bacteria in the intestine, prevent the excessive proliferation of pathogenic bacteria through competitive inhibition, so as to strengthen local intestinal and systemic immunity and enhance intestinal function.[7,19] Probiotic therapy is effective in promoting clinical remission in UC patients, suggesting that the intestinal microbiota is key to the treatment of UC.[20] A previous study showed that the combination therapy using several probiotics such as *Lactobacillus, Streptococcus*, and *Bifidobacterium* could effectively improve the overall outcome of UC patients.[21] However, reliance on only the above probiotics is insufficient to achieve complete restoration of the intestinal flora of patients. Therefore, IMT is a new attempt and breakthrough in the management of UC.

In the present study, patients with IMT had post-treatment levels of TNF-α, IL-1β, IL-17, and IL-23 than those without IMT (P<0.05), suggesting that IMT was effective in mitigating the inflammatory response in the patients.

Table 3 Adverse Events [n (%)]

	Control Group	Research Group	χ^2	P
n	47	47		
Abdominal distention and pain	2	2		
Fever	1	1		
Nausea/vomiting	1	2		
Abnormal liver function	0	1		
Total incidence (%)	8.51%	12.77%	0.447	0.503

Mesalamine plus IMT was associated with significantly higher treatment efficiency (97.8%) versus mesalamine alone (80.85%). Previous study had explored the effects of mesalazine combined with bifidobacterium triple on the levels of intestinal flora, immunoglobulin and calprotectin (Cal), matrix metalloproteinase-9 (MMP-9), and myeloperoxidase in UC, and the results showed that mesalazine combined with bifidobacterium triple revitalizer can enhance the efficacy of UC, improve the composition of intestinal flora, weaken the immune response, and reduce the level of Cal and MMP-9 in the intestine.[22] There were differences with the indicators studied in this study, but the results were similar. Liu et al used IMT treatment in 146 patients with moderate UC and found that patients had a decrease in Pseudomonas species in their intestines after treatment. This suggests that IMT treatment may induce taxonomic modifications of intestinal bacteria in patients and even steer interactions between bacteria, fungi, and viruses in the intestinal tract of patients, but the specific mechanisms require further in-depth clinical investigations.[23] Moreover, significantly lower D-lactate and serum DAO levels were observed after IMT intervention than those with mesalamine alone ($P<0.05$), and mesalamine plus IMT resulted in significantly lower intestinal microbiota scores, colonoscopy scores, and Sutherland index versus mesalamine alone ($P<0.05$), which was consistent with the results by Liu et al,[23] confirming that IMT could effectively improve the level of intestinal flora and intestinal mucosal barrier function in patients. Furthermore, IMT features no significant increase in adverse effects than the control methods.

The current study has the following shortcomings: (1) the number of samples included in this study was relatively small due to physical and environmental factors, which affected the extrapolation of the study findings. (2) The subjects included in this study were all with mild to moderate UC, which may have caused some bias in the study results. (3) There was no long-term follow-up of patients in the present study, which prevented the assessment of prognosis due to the lack of follow-up data on underlying infections, inflammation, immunometabolic diseases, and gastrointestinal disorders. Therefore, future in-depth studies with larger clinical sample sizes and longer follow-up periods are still required.

Conclusion

IMT efficiently ameliorates the intestinal microbiota conditions of UC patients, mitigates inflammatory responses in the body, and facilitates the restoration of intestinal mucosal barrier function, with no significant increase in adverse effects.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Du L, Ha C. Epidemiology and pathogenesis of ulcerative colitis. *Gastroenterol Clin North Am*. 2020;49(4):643–654. doi:10.1016/j.gtc.2020.07.005
2. Kaenkumchorn T, Wahbeh G. Ulcerative colitis: making the diagnosis. *Gastroenterol Clin North Am*. 2020;49(4):655–669. doi:10.1016/j.gtc.2020.07.001
3. Yu YR, Rodriguez JR. Clinical presentation of Crohn's, ulcerative colitis, and indeterminate colitis: symptoms, extraintestinal manifestations, and disease phenotypes. *Semin Pediatr Surg*. 2017;26(6):349–355.
4. Glassner KL, Abraham BP, Quigley EMM. The microbiome and inflammatory bowel disease. *J Allergy Clin Immunol*. 2020;145(1):16–27.
5. Yuan X, Chen B, Duan Z, et al. Depression and anxiety in patients with active ulcerative colitis: crosstalk of gut microbiota, metabolomics and proteomics. *Gut Microbes*. 2021;13(1):1987779.
6. Nusbaum DJ, Sun F, Ren J, et al. Gut microbial and metabolomic profiles after fecal microbiota transplantation in pediatric ulcerative colitis patients. *FEMS Microbiol Ecol*. 2018;94(9):25.
7. Lamb CA, Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut*. 2019;68(Suppl 3):s1–s106.
8. Nishikawa Y, Sato N, Tsukinaga S, et al. Long-term outcomes of antibiotic combination therapy for ulcerative colitis. *Ther Adv Chronic Dis*. 2021;12:20406223211028790.
9. Ryan FJ, Ahern AM, Fitzgerald RS, et al. Colonic microbiota is associated with inflammation and host epigenomic alterations in inflammatory bowel disease. *Nat Commun*. 2020;11(1):1512.
10. Shen ZH, Zhu CX, Quan YS, et al. Relationship between intestinal microbiota and ulcerative colitis: mechanisms and clinical application of probiotics and fecal microbiota transplantation. *World J Gastroenterol*. 2018;24(1):5–14. doi:10.3748/wjg.v24.i1.5

11. Wang J, Zhang C, Guo C, Li X. Chitosan ameliorates DSS-induced ulcerative colitis mice by enhancing intestinal barrier function and improving microflora. *Int J Mol Sci*. 2019;20(22):36.
12. Spiceland CM, Lodhia N. Endoscopy in inflammatory bowel disease: role in diagnosis, management, and treatment. *World J Gastroenterol*. 2018;24(35):4014–4020. doi:10.3748/wjg.v24.i35.4014
13. Tavakoli P, Vollmer-Conna U, Hadzi-Pavlovic D, Grimm MC. A review of inflammatory bowel disease: a model of microbial, immune and neuropsychological integration. *Public Health Rev*. 2021;42:1603990.
14. Karl JP, Armstrong NJ, McClung HL, et al. A diet of U.S. military food rations alters gut microbiota composition and does not increase intestinal permeability. *J Nutr Biochem*. 2019;72:108217. doi:10.1016/j.jnutbio.2019.108217
15. Paone P, Cani PD. Mucus barrier, mucins and gut microbiota: the expected slimy partners? *Gut*. 2020;69(12):2232–2243. doi:10.1136/gutjnl-2020-322260
16. Hou Q, Huang J, Ayansola H, Masatoshi H, Zhang B. Intestinal stem cells and immune cell relationships: potential therapeutic targets for inflammatory bowel diseases. *Front Immunol*. 2020;11:623691. doi:10.3389/fimmu.2020.623691
17. Tatiya-Aphiradee N, Chatuphonprasert W, Jarukamjorn K. Immune response and inflammatory pathway of ulcerative colitis. *J Basic Clin Physiol Pharmacol*. 2018;30(1):1–10. doi:10.1515/jbcpp-2018-0036
18. Ueno A, Jeffery L, Kobayashi T, Hibi T, Ghosh S, Jijon H. Th17 plasticity and its relevance to inflammatory bowel disease. *J Autoimmun*. 2018;87:38–49. doi:10.1016/j.jaut.2017.12.004
19. Akutko K, Stawarski A. Probiotics, prebiotics and synbiotics in inflammatory bowel diseases. *J Clin Med*. 2021;10(11):2466. doi:10.3390/jcm10112466
20. Zhang XF, Guan XX, Tang YJ, et al. Clinical effects and gut microbiota changes of using probiotics, prebiotics or synbiotics in inflammatory bowel disease: a systematic review and meta-analysis. *Eur J Nutr*. 2021;60(5):2855–2875.
21. Koretz RL. Probiotics in gastroenterology: how pro is the evidence in adults? *Am J Gastroenterol*. 2018;113(8):1125–1136.
22. Jiang XE, Yang SM, Zhou XJ, Zhang Y. Effects of mesalazine combined with bifid triple viable on intestinal flora, immunoglobulin and levels of cal, MMP-9, and MPO in feces of patients with ulcerative colitis. *Eur Rev Med Pharmacol Sci*. 2020;24(2):935–942.
23. Liu X, Li Y, Wu K, Shi Y, Chen M. Fecal microbiota transplantation as therapy for treatment of active ulcerative colitis: a systematic review and meta-analysis. *Gastroenterol Res Pract*. 2021;2021:6612970.