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Original Article

Efficacy of faecal microbiota transplantation on ulcerative colitis and its effect on gastrointestinal motility and immune function

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Abstract: Objective: To investigate the efficacy of faecal microbiota transplantation (FMT) in the treatment of ulcerative colitis (UC) and its effect on gastrointestinal motility (GM) and immune function. Methods: A retrospective cohort study was conducted on 47 UC patients. The patients were divided into an observation group (n=17, treated with FMT) and a control group (n=30, treated with conventional treatment) according to the treatment regimen. In the observation group, FMT was used to treat colonic lesions by transplanting colonic bacteria fluid from healthy people. Clinical efficacy, immune function, level of inflammatory factors and gastrointestinal function of the two groups were observed before and after treatment. Results: The total response rates of observation group was 94.12%, which was higher than that of control group (70.00%; P<0.05). After treatment, the contents of CD3+, CD4+ T cells and CD4+/CD8+ ratio were increased, while the content of CD8+ T cells was decreased in both groups compared with those before treatment (all P<0.05); and the contents of CD3+, CD4+ T cells and CD4+/CD8+ ratio in the observation group were higher than those in the control group, while CD8+ T cells showed an opposite trend (P<0.05). The levels of immunoglobulin A, immunoglobulin G and immunoglobulin M as well as interleukin-6, C-reactive protein, tumor necrosis factor-α and motilin were lower than those before treatment in both groups (all P<0.05), and the decreases in the observation group were more significant than those in the control group (all P<0.001). After treatment, cholecystokinin and vasoactive peptide were higher than those before treatment in both groups (all P<0.05), and the increased degree in the observation group was more obvious than that in the control group (all P<0.001). Conclusion: FMT has significant clinical efficacy in the treatment of UC, which may be related to the improvement of immune function, alleviation of inflammatory response and promotion of GM recovery.

Keywords: Faecal microbiota transplantation, ulcerative colitis, immune function, inflammation factor, gastrointestinal motility

Introduction

Ulcerative colitis (UC) is a persistent, chronic and easily recurrent non-specific inflammatory bowel disease, mainly characterized by gastrointestinal symptoms such as abdominal pain, diarrhea, mucopurulent bloody stool, etc. [1-3]. Currently, the annual number of UC patients in the world ranges from 37 to 246/100,000 [4]. In China, the population aged 20-30 years old are more prone to UC, among them females have a higher incidence than males. The incidence of new cases in China is 1.8/100,000 annually and is increasing every year [5]. The pathogenesis of UC is still unclear, and immune inflammatory reaction, intestinal flora dysregulation and intestinal epithelial barrier dysfunction are closely related to the occurrence and development of UC [6].

Intestinal flora dysregulation has attracted more and more clinical attention in the occur-

rence, development and treatment of UC. Previous studies have shown that there are millions of bacterial communities colonized in the human intestine, which play an important role in the normal physiological function of the human body, which involves the regulation of human immunity, metabolism, endocrine regulation, etc. [7, 8]. The relationship between intestinal flora dysregulation and UC is very complex. Previous studies have found that intestinal flora dysregulation is an inducing factor for the occurrence of UC, and UC will further aggravate the occurrence of intestinal flora dysregulation, resulting in a vicious circle. But the mechanism of the interaction between the two is still unclear [9].

At present, the clinical treatment for patients with UC mainly rely on drugs to inhibit inflammation and regulate immunity, but the above drugs has a poor efficacy and is prone to relapse, and long-term use may produce adverse reactions [10, 11]. It has been shown that the application of probiotics or FMT to treat inflammatory bowel disease can improve the clinical symptoms and reduce the inflammatory response of patients. Therefore, the treatment of UC by regulating intestinal flora has been started clinically [12, 13]. However, the application of FMT in the treatment of UC is still at its early stage. Aprevious study performed by Australia scientists have pointed out that FMT could be used in the treatment of UC, but it also indicated that the route, dose, times of administration and safety of treatment of FMT still needs to be studied with large samples [14]. Based on this, this study investigated the clinical efficacy of FMT in the treatment of patients with UC in our hospital and explored the possible mechanism of FMT for treating UC, so as to provide more clinical basis for clinical research.

Materials and methods

General information

This study was approved by the Ethics Committee of our hospital, and 47 UC patients admitted to our hospital from June 2020 to June 2021 were included in this retrospective cohort study. The included patients were aged from 20 to 59 years old, with an average age of 34.2±7.3 years old. Those patients were divided into an observation group (n=17, treated with FMT) and a control group (n=30, treated with conventional treatment) according to treatment methods. In the observation group, FMT was used to treat colonic lesions by transplanting colonic bacteria fluid from healthy people.

Inclusion criteria: (1) Patients who were conformed to the diagnostic criteria for UC established by the Chinese Medical Association [15]; (2) Patients with clear consciousness and free speech; (3) Patients with complete clinical data; (4) Patients whose gastrointestinal motility (GM), inflammation factors and immune indexes were detected before and after treatment.

Exclusion criteria: (1) Patients with incomplete clinical data; (2) Patients with malignant tumor; (3) Patients with complicated infection in other sites during treatment; (4) Patients with duodenal ulcer; (5) Patients with mental disorders.

Methods

Patients in the control group were treated with conventional treatment. Routine treatment regimen: A total of 1.0 g Mesalazine enteric-coated tablets (Jiamusi Luling Pharmaceutical Co., Ltd., Sunflower Pharmaceutical Group, China; Specifications: 0.25 g) were taken orally, 4 times per day. A total of 0.42 g Bifidobacterium triple live capsules (Shanghai Shangyao Xinyi Pharmaceutical Co., Ltd., China; Specifications: 0.21 g) were taken orally, twice a day. Drug administration lasted for 2 months.

Patients in the observation group were given FMT treatment. Details are as follows. (1) Donor selection of faecal microbiota: 1) Donors who did not take antibiotics in the last 3 months; 2) Donors without gastrointestinal diseases or immune diseases; 3) Donors with normal times of daily defecation and normal color of feces; 4) Donors without history of infectious diseases or recent travel to epidemic areas; 5) Donors abstained from irritant and sensitive food for 5 days before providing feces, and whose feces were collected using fresh bags immediately after the first defecation on the same day. Fecal bacteria separation was conducted on the fresh feces according to previous literature [16]. (2) Preparation for patients before FMT: 1) Patients were forbidden to take antibiotics 1 week before operation; 2) Patients abstained from irritant and sensitive food one week before operation; 3) Patients without other infectious diseases recently; 4) Patients had intesti-

nal preoperative preparation with laxatives 1 d before FMT. (3) FMT process: Patients were given intramuscular injection of 10 mg of anisodamine before transplantation to reduce gastrointestinal peristalsis and facilitate the smooth operation of fecal transplantation. Colonoscopy was used to extract colonic faecal bacteria from healthy people or extract bacterial fluid directly from feces, and then the extracts were transplanted to the patient's colon. Details are as follows. A total of 500 mL of bacterial fluid extracted from the feces (60 g) of healthy people was sprayed into the diseased colon of the patient through the colonoscopy biopsy hole. The fecal bacteria liquid should be sprayed evenly as far as possible. The patients were required to lie up for 1 h after the transplantation, and control exhaust and defecation as far as possible [16].

Outcome measures

(1) Clinical efficacy was observed two months after treatment, and it was divided into remarkable effect, effect and no effect. Remarkable effect: Stool routine after treatment showed that the number of white blood cells and red blood cells was basically normal, the intestinal mucosa examination results were normal, and all clinical symptoms disappeared. Effect: After treatment, the patient's clinical symptoms were mild. Stool routine showed that there were still white blood cells and red blood cells, but the number was small. Intestinal mucosa examination showed slight inflammation. No effect: The clinical symptoms of patients were not improved or even aggravated after treatment. Total response rate: Number of cases with (remarkable effect + effect)/total number of cases *100%.

(2) Tr cells and inflammatory factors in peripheral blood were detected. Immune and inflammatory markers were measured before and after treatment. The expression of FITC-labeled anti-human CD3, CD4 and CD8 monoclonal antibodies was detected by FACSCanto II flow cytometry (BD Company, USA), and the CD3+%, CD4+%, CD8+% and CD4+%/CD8+% T cell subsets were compared. Serum levels of immunoglobulin A (IgA), immunoglobulin G (IgG) and immunoglobulin M (IgM) were determined by immunofluorescence assay. Serum and plasma were separated by a centrifuge (Shanghai Jumu Medical Equipment Co., Ltd., China) at 3300 rpm for 15 min. The separated plasma was added into 40 μL of phosphate buffer solution with protease inhibitor (Xiamen Haibiao Technology Co., Ltd., China) and stored at -80°C. The contents of interleukin-6 (IL-6), C-reactive protein (CRP) and tumor necrosis factor-α (TNF-α) were determined by enzyme-linked immunosorbent assay (Shanghai Bairui Biotechnology Co., Ltd., China) with a fully automatic multifunctional enzyme label assay (Thermo, Inc., USA).

(3) GM indexes: The levels of motilin, cholecystokinin (CCK) and vasoactive peptide (VIP) in fasting plasma were determined by immunosorbent assay.

Statistical analysis

SPSS 17.0 statistical software was used for data analysis. Continuous variables were represented by mean ± standard deviation ($\bar{x}\pm sd$); data in accordance with normal distribution and homogeneity of variance were tested by t test and expressed as t; conversely, data were tested by rank sum test and expressed as Z. One-way ANOVA was used to detect whether there were differences among the multiple groups, and Bonferroni method was further used to conduct post-hoc pairwise comparison if there existed a difference. Count data were performed by Pearson chi-square test or Fisher's exact probability method, and were represented by χ^2. $P<0.05$ was considered statistically significant.

Results

Comparison of general information

There was no statistical difference in general information among the two groups (all $P>0.05$), as shown in **Table 1**.

Comparison of clinical efficacy

The total response rates of the observation group was 94.12%, which was higher than that of the control group (70.00%; $P<0.05$). See **Table 2**.

Comparison of Tr cell subsets in peripheral blood

Before treatment, there was no significant difference in the contents of CD3+, CD4+, CD8+ T

Table 1. Comparison of general information ($\bar{x}$±sd)

Item	Observation group (n=17)	Control group (n=30)	χ^2/F	P
Gender (male:female)	7:10	14:16	0.141	0.932
Age (years old)	33.8±7.9	34.6±7.2	0.061	0.941
BMI (kg/m^2)	23.96±2.73	24.06±2.69	0.024	0.976
Course of disease (year)	4.3±1.8	4.2±1.7	0.130	0.878

Table 2. Comparison of clinical efficacy (n, %)

Group	Remarkable effect	Effect	No effect	Total response rate
Observation group (n=17)	10 (58.82)	6 (35.29)	1 (5.88)	16 (94.12)*
Control group (n=30)	11 (36.67)	10 (33.33)	9 (30.00)	21 (70.00)
χ^2		6.214		5.563
P		0.032		0.038

Note: Compared with the control group, *P<0.05.

cells and CD4+/CD8+ ratio between the two groups (all P>0.05). After treatment, the contents of CD3+, CD4+ T cells and CD4+/CD8+ ratio were increased, while the content of CD8+ T cells was decreased in both groups compared with those before treatment (all P<0.05); the content of CD3+, CD4+ T cells and CD4+/CD8+ ratio in the observation group were higher than those in the control group, while CD8+ T cells showed an opposite trend (all P<0.05). See **Table 3**.

Comparisons of immune and inflammatory factors

No difference was found in IgA, IgM and IgG levels between the two groups before treatment (all P>0.05). After treatment, IgA, IgM and IgG in both groups were lower than those before treatment (all P<0.05), and the decrease degree in the observation group was more obvious than that in the control group (all P<0.001). There were similar trends in CRP, TNF-α, and IL-6 levels (all P<0.05). See **Tables 4** and **5**.

Comparison of GM indexes

After treatment, the levels of motilin in both groups were lower than those before treatment (P<0.05), and the decrease degree of the observation group was more significant than that of the control group (both P<0.001). After treatment, CCK and VIP in both groups were higher than those before treatment (all P<0.05), and the level in the observation group was higher than that in the control group (all P<0.001). See **Table 6**.

Discussion

The pathogenesis of UC is still unclear. Studies have shown that the disorder of intestinal microorganisms causes immune dysfunction and inflammatory response, which are closely related to the occurrence and development of UC [17]. It has been reported that intestinal microorganisms can synthesize important metabolites in human body to stimulate the formation of intestinal mucosal immune function, which is conducive to preventing the invasion of bacteria and maintaining the stability of the body's internal environment and intestinal microecology [18]. Studies on the intestinal microecology of UC patients found that the diversity of intestinal microflora was significantly decreased, with increased facultative anaerobe and less obligate anaerobe [19, 20]. Although oral probiotics treatment of UC had certain effect, but great individual differences exist [21, 22].

Compared with oral probiotics, FMT for UC has a more direct effect on the diseased intestinal tract. Also, it enables patients to quickly establish a new bacterial balance system in the intestinal flora, which is beneficial to regulate intestinal immunity, reduce inflammatory response, and promote the repair of damaged intestinal mucosa [23]. A randomized, double-blind clinical study on FMT for UC in 2018 found that FMT was beneficial to the repair of intestinal mucosa in patients, and the improvement of intestinal flora was correlated with disease recovery [24]. An oversea randomized controlled study on patients with recurrent Clostridium difficile infection treated with FMT versus antibiotics alone found that the improvement rate of diarrhea symptoms in patients treated with FMT was up to 81.25%, while that was only 25% in patients treated with antibiotics alone [25]. Another study showed that the clinical

Table 3. Comparison of Tr cell subsets in peripheral blood ($\bar{x}$±sd)

Item	Observation group	Control group	t	P	Observation group	Control group	t	P
	Before treatment	Before treatment			After treatment	After treatment		
CD3+ (%)	55.37±9.96	55.62±10.11	0.004	0.996	64.36±8.53*	58.55±7.82*	3.811	0.028
CD4+ (%)	31.83±6.21	31.65±6.24	0.005	0.995	39.38±7.93*	34.42±7.22*	3.216	0.047
CD8+ (%)	23.81±2.45	23.83±2.67	0.002	0.998	21.53±1.82*	22.92±1.73*	4.334	0.018
CD4+/CD8+	1.32±0.33	1.34±0.32	0.222	0.978	1.85±0.38*	1.57±0.41*	4.045	0.023

Note: Compared with before treatment within the same group, *P<0.05.

Table 4. Comparison of immune factors ($\bar{x}$±sd)

Item	Before treatment		After treatment	
	Observation group (n=17)	Control group (n=30)	Observation group (n=17)	Control group (n=30)
IgA (g/L)	5.01±1.03	5.02±0.98	1.44±0.71***,###	3.55±0.86**
IgM (g/L)	2.42±0.73	2.33±0.73	1.27±0.45**,###	1.72±0.57*
IgG (g/L)	20.78±3.88	21.02±3.56	12.32±2.23***,###	16.71±2.57***

Note: Compared with the same group before treatment, *P<0.05, **P<0.01, ***P<0.001; compared with the control group after treatment, ###P<0.001. IgA: immunoglobulin A; IgG: immunoglobulin G; IgM: immunoglobulin M.

Table 5. Comparison of inflammatory factors ($\bar{x}$±sd)

Item	Before treatment		After treatment	
	Observation group (n=17)	Control group (n=30)	Observation group (n=17)	Control group (n=30)
CRP (mg/L)	6.85±1.82	6.74±1.77	4.82±1.54**,###	5.72±1.51*
TNF-α (μg/mL)	123.94±18.71	124.04±18.81	87.01±15.04***,###	104.26±16.72***
IL-6 (μg/mL)	351.48±36.82	352.71±37.23	275.47±26.92***,###	318.94±31.55***

Note: Compared with the same group before treatment, *P<0.05, **P<0.01, ***P<0.001; compared with the control group after treatment, ###P<0.001. CRP: C-reactive protein; TNF-α: tumor necrosis factor-α; IL-6: interleukin-6.

Table 6. Comparison of gastrointestinal motility indexes ($\bar{x}$±sd)

Item	Before treatment		After treatment	
	Observation group 1 (n=17)	Control group (n=30)	Observation group (n=17)	Control group (n=30)
Motilin (pg/mL)	134.22±13.24	133.87±12.54	100.23±9.12***,###	109.73±9.78***
CCK (pg/mL)	103.25±10.32	104.22±10.65	125.82±11.29***,###	115.34±10.73***
VIP (pg/mL)	52.22±3.87	51.34±3.98	76.76±5.39***,###	64.59±5.94***

Note: Compared with the same group before treatment, ***P<0.001; compared with the control group after treatment, ###P<0.001. CCK: cholecystokinin; VIP: vasoactive peptide.

response rate in 18 UC patients treated with FMT within one week was up to 79%, suggesting that FMT treatment is relatively safe [26]. However, some clinical studies have indicated that although FMT can correct the intestinal flora dysregulation in patients with UC, it has not been effectively alleviated in clinic [27, 28]. This study compared the changes of clinical effects on UC patients before and after treatment, and evaluated the clinical efficacy of FMT in the treatment of UC. The results showed that the clinical response rate of the observation group treated with FMT was higher than that of the control group, suggesting that FMT has certain advantages in the treatment of UC. It may be that FMT treatment can maximize the improvement of intestinal microecological environment, regulate the balance of intestinal flora, maintain the balance of inflammatory factors in the body cells, and promote the improvement of therapeutic effect.

Previous studies have found that intestinal immune response is activated under the influence of intestinal flora and psychological factors, resulting in increased intestinal mucosal

permeability, thereby leading to impaired intestinal barrier function [9]. Due to the increased intestinal mucosal permeability, pro-inflammatory substances can induce the immune response of the body through the intestinal mucosa, and eventually lead to the imbalance of intestinal mucosal immune balance, causing the occurrence of diseases [29, 30]. In the study on UC patients, it is believed that intestinal flora may have the following effects on the development of patients with UC. (1) Probiotics are significantly reduced in patients with UC after intestinal flora dysregulation, and the role of probiotics is to antagonize the binding sites of pathogenic microorganisms and compete for nutrients to inhibit bacteria, as well as protect the intestinal mucosal barrier [31]. (2) The decreased number of probiotics also brings the increased number of pathogenic bacteria. The virulence and invasion of pathogenic bacteria can damage the intestinal mucosa, and also play the role of intestinal bacterial translocation, increasing the risk of intestinal diseases [30]. (3) Intestinal microflora dysregulation disrupts the intestinal immune balance. Studies have found that intestinal microflora can regulate the function of immune cells; intestinal microflora dysregulation leads to the release of inflammatory factors, disruption of normal intestinal immunity, activation of abnormal immune responses in the intestine, and damage to intestinal mucosa and intestinal tissues [32]. Previous researches have indicated that intestinal flora can also regulate inflammatory factors; for example, Lactobacillus can promote immune function while inhibiting inflammatory response, as well as increase the secretion of anti-inflammatory factors [33]. It is reported that increased secretion of inflammatory factors in the intestinal tract results in the disturbance of GM, and the level of inflammatory factors is closely related to changes in certain specific intestinal flora [34, 35]. In this study, the relevant mechanisms of FMT treating UC were further explored, and the immune function, inflammatory factors and GM indexes of patients were observed before and after treatment. We found that after FMT treatment, the improvement effect of peripheral blood Tr cells was better, and FMT treatment could reduce the level of inflammatory factors. Immune function and the level of inflammatory factors have important significance for intestinal function.

In terms of GM, motilin is a peptide secreted by the duodenum and jejunum, which promotes gastrointestinal peristalsis by stimulating cholinergic neurons [34]. CCK is a polypeptide hormone composed of 33 amino acids. It is the first gastrointestinal hormone that causes the sense of anorexia. Its secretion is caused by the consumption of nutrients such as protein, fat and carbohydrate, and CCK is mainly secreted by L cells of small intestine mucosa. Studies have found that CCK and its receptors are widely present in the gastrointestinal tract and central nervous system, and the main receptors are CKK1 and CCK2 receptors with different distribution and function [36]. CCK1 receptor is mainly distributed in the gastrointestinal system, while CCK2 receptor is mainly expressed in the central nervous system. As a gastrointestinal hormone and neuropeptide, CCK has the functions of regulating gastrointestinal creep, promoting the contraction of gallbladder and gastrointestinal smooth muscle, depressing gastric acid secretion, inhibiting postprandial gastric emptying and restraining colonic transport, which are mainly accomplished through CCK1 receptors. Studies have reported that both endogenous and exogenous CCK can inhibit gastric empty and intestinal transport in rats [37]. VIP is a kind of polypeptide found in the gastrointestinal tract, which can promote the decomposition of glycogen, stimulate intestinal secretion and reduce lipid. VIP plays a dual role of neurotransmitter and gastrointestinal hormone in the body. VIP can affect intestinal peristalsis through binding with relevant receptors, and its expression is closely related to gastrointestinal function [38]. This study found that the improvement of GM related hormone levels in the observation group treated with FMT was better than that in the control group, suggesting that FMT treatment for UC may be related to the improvement of gastrointestinal hormone levels.

Intestinal floras have effects on gastrointestinal motility and gastric hormones. Previous studies have shown that intestinal flora may be directly involved in regulating the development of the intestinal nervous system after birth of embryo [39]. Intestinal flora may also regulate gastrointestinal motility by changing the number of neurons in the intestinal nervous system and the proportion of different types of neurons [40]. Another study showed that intestinal flora

and its metabolites signal intestinal neurons by influencing intestinal endocrine cells to secrete gastrointestinal hormones, thus regulating gastrointestinal motility [41]. Intestinal flora can activate mucosal immune cells including macrophages, which can react on intestinal flora. It is suggested that intestinal flora and macrophages in muscular layer can interact and influence gastrointestinal motility, in which bone morphogenetic protein 2 may play a key role [42]. In addition, Zhao et al. used feces of children with irritable bowel syndrome to make fecal bacteria liquid and gave the liquid to mice by gavage. They found that the propulsion rate of small intestine, motitin and gastrin of mice were significantly reduced, and the expression of acid sensitive ion channels in the small intestine and colon were found, suggesting that intestinal flora may be involved in the regulation of gastrointestinal motility [43]. Previous studies using rodents as models showed that the secretion of ghrelin and cholecystokinin may also be closely related to intestinal flora [44]. Another study showed that introducing the intestinal flora of healthy adult pigs to piglets at an early stage of growth can accelerate the growth and intestinal development of host piglets, change the structure of intestinal flora, and increase the diversity of intestinal flora. FMT increased the level of cholecystokinin in serum of piglets. Besides, the expression level of intestinal hormones also fluctuates due to changes in intestinal flora caused by FMT [45].

In addition, this study revealed that FMT could improve GM indexes. We found that FMT treatment could significantly improve the immune function, reduce inflammatory response and promote GM recovery in the UC patients. FMT for treating UC may be related to immune inflammation and GM, which is consistent with the above research results. In this study, the clinical symptoms in patients with UC whose lesions were in the colon were improved after FMT treatment, and favorable improvements were also showing in inflammation, immune function and GM recovery.

This study exists limitations. It was a retrospective cohort study with a small sample size; therefore, a multi-center prospective study should be further conducted to observe the efficacy of FMT in the treatment of UC.

In conclusion, FMT has significant clinical efficacy in the treatment of UC, which may be related to the improvement of patients' immune function, reduction of inflammatory response and promotion of GM recovery.

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Disclosure of conflict of interest

None.

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