Research Article

To Determine the Frequency of Clinical Remission Induction with Versus Without Fecal Microbiota Transplant in Treatment of Active Ulcerative Colitis

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Abstract

Background: Ulcerative colitis is a long lasting inflammatory disease of the intestines that gets worse over time.

Objective:. The goal of this study was to compare the success rates of inducing clinical remission in patients with active Ulcerative Colitis who underwent treatment with or without Fecal Microbiota Transplant.

Methods: It was Randomized Controlled Trial, which was done in Department of Gastroenterology / Medical Unit 2, AIMC/ Jinnah Hospital, Lahore. Study duration was eighteen months from 01-01-2021 to 30-06-2022.The research included 90 patients who were randomly assigned to two groups. Standard Ulcerative Colitis therapy was given to both groups. Patients in group A received once-weekly faecal microbiota transplant for a period of six weeks. Patients in group B had weekly water enemas for same period. All patients underwent colonoscopy and Mayo score was noted before treatment, and after 6 weeks of treatment. Clinical remission was labeled if patients achieved Mayo score 2 after treatment.

Results: Group A (Treatment) had a mean age of 39.31 ±13.45 and group B (Control) had a mean age of 38.59 ±12.11 (p=0.52). Duration of ulcerative colitis in group A was 8.08±2.64 weeks and in group B was 9.00±2.62 weeks (p=0.76). Pre-treatment Mayo score in groups A and B, were 8.29±1.91in and 8.73 ±1.61 respectively (p=0.15). Post-treatment in group A, the Mayo score was 3.71± 2.22, whereas in group B, it was 5.07± 1.75 (p=0.003). Remission was achieved in 24.44% (n=11) in fecal microbiota transplant group and 8.88% (n=4) in control group. (p=0.003).

Conclusion: When compared to the control group, FMT significantly induces remission in patients with active UC.

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Introduction

Ulcerative colitis is a long lasting inflammatory disease of the intestines that gets worse over time. It causes loose stools, bloody diarrhea, abdominal pain, weight loss, joint pain, and anaemia.[1,2] Steroids, 5ASA compounds, immune modulators, and biologicals are only a few examples of the many therapeutic choices available for treatment. The gut microbiota has been shown to have a crucial role in intestinal inflammation, and there is substantive data to back this notion.[3] Studies have increasingly shown that the dysbiosis of the gut microbiota is essentially involved in the pathophysiology of ulcerative colitis. In recent years, fecal microbiota

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transplantation (the administration of a fecal solution generated from a healthy donor(s) into the gastro-intestinal tract of a patient with disease) has garnered increasing interest and become a significant therapeutic strategy.[4] It is a non-immunosuppressive approach of dealing with the microbial perturbations that cause the disease.[5] The three main components of fecal microbiota transplantation (FMT) are donor selection, donor substance preparation, and fecal microbiota transplantation delivery. [6,7]

FMT has several advantages over other therapeutic microbial remedies (such as antibiotics, probiotics, and prebiotics) as it offers a unique functional ecosystem made up of full range of microbial organisms from a healthy person. Consequently, it may be able to correct dysbiosis and functional disturbances that are crucial to the pathogenesis of inflammatory bowel disease. Due to its expanding usage in the treatment of Clostridium difficile infection,FMT is gaining wider recognition and acceptance.[8] However, many questions remain unanswered about its utility in ulcerative colitis.[9] FMT can quickly reduce clinical symptoms and provides treatment benefits in patients with active UC.[10,18-20] Few studies have evaluated the sustained long term remission brought about by FMT. In one study, remission in ulcerative colitis was found in 24% of cases with FMT and in 5% of cases without it (p 0.05). Another study indicated that among people with ulcerative colitis, 30.4% achieved remission after receiving FMT, compared to 20% of those who did not (p>0.05). [11]

The aim of this study was to examine Ulcerative Colitis clinical remission with and without FMT. Literature showed that the fecal Microbiota Transplant can help in response and effective remission of ulcerative colitis. But conflicting data has been retrieved from literature and that data creates ambiguity, whether to consider Fecal Microbiota Transplant as an effective mode of treatment for ulcerative colitis. Moreover, there was no local data available in this regard. Therefore, we carried out this research to identify the role of fecal microbiota transplant in remission of ulcerative colitis in our local setting. So that we may apply the results of this study in diverse communities in the future and add Fecal Microbiota Transplant as a cost effective mode of treatment for patients of ulcerative colitis.

Methods

This Randomized Controlled study was carried out in Medical Unit II, Department of Gastroenterology, Jinnah Hospital, Lahore. The trial lasted for 18 months, from January 1, 2021, to June 30, 2022. With a 5% significance level, an 80% power of the study, and the assumption of the expected percentage of remission in ulcerative colitis, which is 24% with fecal microbiota transplant and 5% without, a sample size of 90 cases is determined, 45 in each group.[13] Non-probability, consecutive sampling was used in the sampling process. Patients (Recipients) with ulcerative colitis (as per operational definition) between the ages of 16 and 75 were involved in the trial and randomly assigned to Group A (Fecal Microbiota Transplant) or Group B (Control). Before FMT, recipients withheld their antibiotics for at least 48 hours. It was done to prepare the recipient's bowels with a polyethylene glycol solution. Additionally, recipients underwent testing for blood-borne diseases such Hepatitis B and C, HIV, syphilis, CMV, etc. Patients who were neutropenic, pregnant, severely immunosuppressed, critically unwell, had uncontrolled concomitant conditions, or needed antibiotics were not eligible for FMT. The Jinnah Hospital OPD was used to choose healthy donors for fecal matter who met the inclusion criteria of being between the ages of 25 and 60years, being in excellent health, and not having used probiotics, antibiotics, antifungal, or antiviral medication during the previous three months. Patients taking acid suppressive therapy (PPI, antacids, H2-receptorantagonists), anti-inflammatory agents, antiplatelets or anticoagulation during the previous month were also excluded, as were patients with sepsis, hepatic encephalopathy, corrosive intake, Helicobacter Pylori infection, malabsorption disorders, inflammatory bowel disease, celiac disease ,previous history of radiation to abdomen and family history of colorectal cancer.

After getting ethical approval from institution 90 patients from the OPD of Jinnah Hospital Lahore who met the eligibility requirements were enrolled in the study. These individuals were newly diagnosed with mild to moderate Ulcerative colitis within three months and receiving standard treatment (Oral 5-ASA, steroids and azathioprine) The informed consent was obtained. Then, using the lottery mrthod, patients were divided into two groups (A & B). Name, age, sex, BMI, diabetes, hypertension,

smoking history (>5 pack years), and ulcerative colitis duration were collected as demographic data.

Patients in Group A were given an enema once a week for six weeks in the hospital by paramedical staff, consisting of 50 g of stool from a single healthy donor suspended in 50 ml of normal saline. The retention time was atleast 20 minutes. Group B received a 50 mL water enema. Colonoscopy was done and Mayo scores were recorded both before and after therapy at 6 weeks. Patients with a Mayo score of ≤ 2 were considered to be in clinical remission (as per operational definition). A premade annexure was used to document all of this data.

Results

SPSS version 22 was used for analysis of the data. Age, the duration of the ulcerative colitis, BMI, and the Mayo scores before and after therapy were among the quantitative variables that were presented as mean ±standard deviation. The frequency and proportion of certain qualitative variables, such as gender, diabetes, hypertension, smoking, and remission were presented in form of frequency and percentages. The chi-square test was used to compare the rates of remission in the two groups. P-values ≤0.05 were considered significant. Age, gender, BMI, diabetes, hypertension, ulcerative colitis duration, and smoking status were stratified in the data. After stratification, the two groups were compared for remission using the chi-square test for each stratum.

In group A, the age distribution was 39.31±13.45 years, while in group B, it was 38.59±12.11 years (p=0.52). The distribution of ulcerative colitis duration was 8.08±2.64 weeks in group A and 9.00±2.62 weeks in group B (p=0.76). In group A, the BMI was assessed to be 26.62± 3.17 kg/m2, while in group B, it was 26.89 3.48 kg/m^2 (p=0.42). Pre-treatment Mayo score in groups A and B, was 8.29 ±1.91 and 8.73± 1.61, respectively (p=0.15). The Mayo score following therapy was 3.71± 2.22 in group A and 5.07 ±1.75 in group B (p=0.003). In group A, 53.33% of the patients (n=24) were male, compared to 46.67% (n=21) of the patients who were female, and 60% (n=27) of the patients were male compared to 40% of the patients in group B (p=0.52) . There were 26.66% (n=12) diabetic individuals in group A and 24.44% (n=11) in group B. (p=0.8). Patients with hypertension were 8.88% (n=4) in group A and 13.33% (n=6) in group B, respectively (p=0.334). In group A, smoking was prevalent (8.88%; n = 4) while in group B, it was 24.4%; n = 11. (p=0.048). In group A, the frequency of remission was 24.44% (n=11), while in group B, it was 8.8% (n=4). (p=0.003).

Table 1: *Distribution of Age Group, Duration of Ulcerative Colitis, BMI, Diabetes Mellitus, Hypertension , Cigarette Smoking, pre and post-treatment Mayo score N=90*

Variables		Group A Mean±SD	Group B Mean±SD	p value
Age group	16-40 years	28(62.22)	25(55.55%)	0.52
	41-75 years	17(37.78%)	20 (44.45%)	
	Total	45 (100.0%) Mean±SD= 39.31±13.45 years	45 (100.0%) Mean±SD = 38.59±12.11 years	
Gender	Male	24 (53.33%)	27(60.00%)	0.52
	Female	21 (46.67%)	18 (40.00 %)	
	Total	45 (100.0%)	45 (100.0%)	
Duration of Ulcerative colitis (weeks)		8.08±2.64 weeks	9.00±2.62 weeks	0.76
BMI (kg/m2)		26.62±3.17 kg/m^2	26.89±3.48 kg/m^2	0.42
Diabetes Mellitus	Yes	12 (26.66%)	11 (24.42%)	0.8
	No	35 (73.34%)	35 (75.58 %)	
	Total	45 (100.0%)	45 (100.0%)	
Hyper-tension	Yes	4(8.88%)	6 (13.33%)	0.334
	No	41 (91.12%)	39 (86.67%)	
	Total	45 (100.0%)	45 (100.0%)	
Smoking	Yes	4(8.88%)	11 (24.44%)	0.048
	No	41 (91.12%)	34 (75.55 %)	
	Total	45 (100.0%)	45 (100.0%)	
Pre-treatment Mayo score		8.29 ±1.91	8.73 ±1.61	0.15
Post-treatment Mayo score		3.71 ±2.22	5.07 ±1.75	0.003
Remission achieved	Yes	11 (24.44%)	4 (8.88%)	0.003
	No	34 (76.56%)	41 (91.12%)	
	Total	45 (100.0%)	45 (100.0%)	

Table 2: *Stratification for Remission Achieved in Both Groups with Respect to Age Using Chi-Square Test (N= 90)*

Variable		Remission achieved	Groups Group A	Group B	Total	P value	
Age group	16-40 years	Yes	6	2	8	0.17	0.048
		No	22	23	55		
	41-75 years	Yes	5	2	7	0.13	
		No	12	18	30		
Gender	Male	Yes	5	2	7	0.16	0.048
		No	19	25	44		
	Female	Yes	6	2	8	0.18	
		No	15	16	31		

BMI	17-25 kg/m^2	Yes	4	2	6	0.46	0.048
		No	13	13	26		
	>25 kg/m^2	Yes	7	2	9	0.05	
		No	21	28	49		
Diabetes Mellitis	Yes	Yes	3	1	4	0.31	0.048
		No	9	10	19		
	No	Yes	8	3	11	0.089	
		No	25	31	56		
Hyper-tention	Yes	Yes	4	2	6	0.15	0.048
		No	3	7	10		
	No	Yes	7	2	9	0.09	
		No	31	34	65		
Duration of Ulcerative Colitis	1-8 weeks	Yes	6	2	8	0.19	0.048
		No	21	21	42		
	>8 weeks	Yes	5	2	7	0.12	
		No	13	20	33		
Cigarette Smoking	Yes	Yes	3	1	4	0.075	0.048
		No	4	11	15		
	No	Yes	8	3	11	0.165	
		No	30	30	60		

Discussion

In order to combat the disease's abnormal immune response, most current treatments for Ulcerative Colitis (UC) aim to reduce inflammation. However, such medicines are being met with growing skepticism from both physicians and patients, who see biologics as posing an elevated risk of infections, cancers, considerable costs, and loss of response.[12,13,17] The concept of FMT has piqued the public's interest, and this strategy is being considered for a variety of disorders, including UC. The approach's efficacy may also be donor-dependent, which may explain why some cases yielded promising results while others had unsatisfactory outcomes.[14,15] The benefit was not much, but our criteria for treatment success were increasingly strict than those used in majority of trials and the FMT remission rates were in line with metrics for novel biologic therapy.[17,23,24] This trial examined the effectiveness of FMT in active states of UC and found that it induces remission in a significant proportion of patients (24.44%; n=11). Similar response (7/23, 30%) was seen by Rossen et al. at 12 weeks in patients receiving two doses of aerobically processed donor stools that had been given three weeks apart. Due to the substantial response seen in control group (5/25, 20%) receiving autologous stool, this study did not reach statistical significance.[18,29]

Another study by Dang et al. found that FMT significantly reduced the severity of UC. Twelve patients got FMT; eleven of them responded clinically, and five maintained remission at 52 weeks of follow-up. Only one patient did not respond to FMT.[25,30] In order to hasten the colonization of the recipient's microbiome with donor microbes, many transplant protocols advise administering antibiotics alongside intestinal lavage prior to the transplantation.[26] We did not implement this approach as there is a lack of evidence to support it at the present time, and the results of the trial would be more difficult to interpret if this combination had any effect on the activity of UC. In contrast to the fact, that smoking is assumed to be a protective factor in emergence of UC, we had found that in maintaining the remission, non-smokers had more proportion both in FMT group and control group. It is unclear whether fresh or frozen thawed fecal samples should be used for FMT. Some studies suggest frozen-thawed stools tended to function better, albeit assessing this is complicated by the fact that the majority of treatment successes were donor-specific. Retention enemas, nasoduodenal route and colonoscopies have all been used in studies evaluating FMT in different diseases.[26-30] We chose the retention enema as in one study it was found more successful than other routes and as UC is characterized by a problem that begins distally but can extend proximally.[4] We believe that the microbiota dysbiosis in UC is likely to commence in the rectum and it may be best targeted by retention enema.[31,32]

The study's sample size is small, and it is yet unclear how much FMT would affect UC. This represents a study limitation. To get a more reliable conclusion, a study with a bigger sample size should be carried out. In individuals with UC, FMT was able to elicit and sustain remission within a limited observation. There haven't been many studies looking at how often FMT should be performed in UC to maintain long-term therapeutic benefits. According to this study, individuals with UC may be provided a subsequent course of FMT a few months after the first course to maintain long-term advantages. In this regard, more research is necessary. Because of these findings, doctors will start considering sequential FMT as a long-term therapy plan for UC. The key merit of our study is that it presents intriguing data suggesting that modifying the intestinal microbiota may be helpful for treating UC.

Conclusion

We came to the conclusion that addition FMT to standard therapy is more effective than standard treatment alone in inducing remission in patients with active UC.

Ethical Approval: The Ethical review board of Allama Iqbal Medical College approved the study vide letter No. Ref No: 84th / ERB.

Conflict of Interest: The authors declare no conflict of interest.

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Authors' Contribution:

AAB: conceived the idea, defended the ethical approval, data acquisition and interpretation, manuscript writing and final approval of the draft

SS: Supervised all steps and critical review of the article

MNA: Data collection and initial draft of manuscript

MG: Critically review for important intellectual contents

MNY: Data interpretation, proof reading and approval of final draft

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