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Evaluation of the Role of Fecal Microbiota Transplantation in The Management of Ulcerative Colitis in Egyptian Patients

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Abstract

Background: Fecal Microbiota Transplantation (FMT) is a novel form of therapeutic microbial manipulation aims to restore the intestinal microbiota in diseased individuals by transferring intestinal microbiota of healthy donors. We aimed to establish the efficacy of multi donor fecal microbiota transplantation in active ulcerative colitis (UC) in Egyptian patients.
Subject and Methods: known UC patients (n-50) were divided in two groups, Group one included 25 patients who treated with medical treatment alone and then follow up was done for 24 weeks. Group two included 25 patients who treated with medical treatment and underwent FMT via complete colonoscopy every three weeks until the 9th week and then follow up was done for the 24th week by clinical picture, laboratory investigation ,complete colonoscopy at 0, 3, 6, 9, 18 and 24 weeks of study.
Results: Clinical remission was achieved in 18 patients (72%) of group II compared to only 5 patients (20%) of group I achieved clinical remission (p value=0.001). Reduction in leucocytic count was in group II(5.8) rather than group I(6.2) (p value=0.008). Improvement in anemia was better in group II(12.4) than group I(11.9) (p value=0.027).
Conclusion: FMT appears to be effective for induction of remission in UC, Further studies are needed to explore its feasibility, efficacy and safety as a maintenance agent.
Keywords: Fecal,micrbiota; transplantation; ulcerative; colitis.

INTRODUCTION

Ulcerative colitis (UC) is a chronic, relapsing and remitting, inflammatory disease of the colon occurring at the interface between the luminal contents and the mucosal immune system.[1]

Although Most of the treatments for UC target the immune system, number of patients continue to have inadequate disease control.2The gut microbiota in healthy individuals is known to provide a number of health benefits to the host, relating to pathogen protection, nutrition, metabolism, and the immune system.3 The role of the gut flora in the pathogenesis of Inflamatory bowel disease (IBD) has been increasingly investigated, and it is now clear that a "dysbiosis" which is an unfavorable alteration of the composition and function of the gut microbiota, exists in IBD that possibly leads to an abnormal immune response which alters host−microbiota interaction and the host immune system.3 Due to the pro-inflammatory role of dysbiosis, fecal microbiota transplantation (FMT) has been recently advocated as a possible additional measure to improve the outcome of IBD. FMT is the transfer of fecal material containing bacteria and natural antibacterial from a healthy individual into a diseased recipient. Previous terms for the procedure include fecal bacteriotherapy, fecal transfusion, fecal transplant, stool transplant, fecal enema, and human probiotic infusion (HPI). Because the procedure involves the complete restoration of the entire fecal microbiota, not just a single agent or combination of agents, these terms have now been replaced by the new term fecal microbiota transplantation.5 FMT has been clinically adapted to recurrent Clostridium difficile infection (CDI), and the efficacy of FMT for CDI has been established with a high cure rate of >90% in clinical trials.6 Number of studies, including randomized controlled trials, systematic reviews, and meta-analyses suggest that FMT is effective in the treatment of patients with active UC.7

SUBJECT AND METHODS

A case control study was carried out to find the efficacy of FMT in patients with ulcerative colitis. This study was conducted on 50 patients who fulfilling the designed inclusion criteria. The study was carried out from

Outpatient Clinic and Inpatient Units of Hepatogastroenterology and Infectious Diseases department, Faculty of Medicine, Al- Azhar University Hospitals (Al-Hussein & Sayed Galal Hospitals) from May 2016 to May 2018.

We included Egyptian patients, age ≥18 years with active UC patients confirmed diagnosis by using conventional clinical, endoscopic, radiological and histopathological criteria after informed consent was taken.

We excluded patients with indeterminate colitis, Major comorbid chronic disease eg CLD, a history of previous malignant diseases, Pregnancy, Irritable bowel syndrome, History of major gastrointestinal surgical procedures especially resection anastomosis operation, Recent antibiotic use (the last two weeks) and Patients refuse to participate in the study.

Donors:

Age ≥18 years, no antibiotic therapy within the past 3 months, Negative history for intestinal diseases or recent gastrointestinal infections, autoimmune or other immune-mediated diseases, or any kind of malignancies, Chronic hepatitis B and C, human immunodeficiency virus, cytomegalovirus, and syphilis were excluded.

Preparation of Donor Stool:

Donors underwent a mild colonic lavage using polyethylene glycol before stools were collected in special vessels, the stool weighing 50 to 100 g was diluted with sterile normal saline (200–350 mL) and filtered through sterile gauze twice to remove crude components. A total of 300 to 500 mL of the extracted suspension containing the donor's intestinal flora was placed into 20-mL syringes. An aliquot of the original donor stool was frozen at enrollment for further analysis of the transferred microbiota alone (oral 5-aminosalicylates (3 grams per day) until activity subsided then maintenance dose 500 mg twice daily) and follow up was done for the 24th week of study and Group II include 25 patients who treated with medical treatment and underwent FMT via complete colonoscopy every three weeks until the ninth week and then follow up was done for the 24th week of study.

Follow up of the patients were done by clinical evaluation, laboratory investigations and colonoscopy at 0, 3, 6, 9, 18 and 24 weeks of study and measuring endoscopic disease activity according Mayo clinic score for activity index for patients of UC.

Statistical analysis:

Data were analyzed using Statistical Program for Social Science (SPSS) version 15.0. Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage.[8]

RESULTS

Variables		Group I (N = 25)		Group II (N = 25)		P-value
Disease extension	Proctosigmoiditis	3	12%	2	8%	0.73 NS
	Lt sided colitis	20	80%	22	88%	
	Pan-colitis	2	8%	1	4%	

Table 1: comparison between studied groups as regard extension of disease

Variables / Group I		Baseline (N = 25)	3 weeks (N = 25)	6 weeks (N = 25)	9 weeks (N = 25)	18 weeks (N = 25)	24 weeks (N = 25)	p-value
Hb (g/dl)	**Mean**	9.6	9.8	10.2	10.4	10.9	11.9	**< 0.001 HS**
	±SD	0.5	0.5	0.5	0.5	0.6	0.6	
WBCs ($x10^3$/cmm)	**Mean**	8.4	8.9	8.0	7.3	6.8	6.2	**< 0.001 HS**
	±SD	1.0	0.5	0.4	0.4	0.4	0.3	
ESR (mm/hour)	**Mean**	35.2	29.9	24.6	20.5	10.2	8.2	**< 0.001 HS**
	±SD	7.0	5.9	4.9	4.0	2.0	1.5	
CRP (mg/dl)	**Mean**	29.8	19.4	13.1	10.5	5.1	3.0	**< 0.001 HS**
	±SD	5.3	3.4	2.6	2.0	1.1	0.5	

Table 2: comparison between laboratory data follows up in group I.HS: p-value < 0.001 is considered highly significant

Variables / Group II		Baseline (N = 25)	3 weeks (N = 25)	6 weeks (N = 25)	9 weeks (N = 25)	18 weeks (N = 25)	24 weeks (N = 25)	p-value
Hb (g/dl)	Mean	9.4	9.8	10.4	10.7	11.1	12.4	**< 0.001 HS**
	±SD	0.5	0.5	0.6	0.6	0.6	0.7	
WBCs ($x10^3$/cmm)	Mean	8.3	8.7	7.8	7.1	6.6	5.8	**< 0.001 HS**
	±SD	1.1	0.5	0.5	0.6	0.5	0.7	
ESR (mm/hour)	Mean	33.8	28.7	22.7	18.5	9.1	7.5	**< 0.001 HS**
	±SD	7.5	6.4	5.1	4.0	2.0	1.7	
CRP (mg/dl)	Mean	30.3	19.7	10.9	9.7	4.6	2.7	**< 0.001 HS**
	±SD	6.1	3.9	2.4	1.8	1.0	0.6	

HS: p-value < 0.001 is considered highly significant.
Table 3: comparison between laboratory data follows up in group II.

Group I / Variables		Baseline (N = 25)		3 weeks (N = 25)		6 weeks (N = 25)		9 weeks (N = 25)		18 weeks (N = 25)		24 weeks (N = 25)		p-value
Stool frequency	**0**	0	0%	0	0%	0	0%	2	8%	5	20%	11	44%	**< 0.001 HS**
	1	0	0%	0	0%	4	16%	6	24%	10	40%	4	16%	
	2	0	0%	4	16%	7	28%	7	28%	6	24%	10	40%	
	3	25	100%	21	84%	14	56%	10	40%	4	16%	0	0%	
Rectal Bleeding	**0**	0	0%	0	0%	0	0%	1	4%	4	16%	8	32%	**< 0.001 HS**
	1	0	0%	0	0%	3	12%	6	24%	6	24%	7	28%	
	2	0	0%	3	12%	8	32%	6	24%	7	28%	7	28%	
	3	25	100%	22	88%	14	56%	12	48%	8	32%	3	12%	
Mucosal app. At endoscope	**0**	0	0%	0	0%	0	0%	2	8%	5	20%	10	40%	**< 0.001 HS**
	1	0	0%	0	0%	4	16%	6	24%	10	40%	3	12%	
	2	0	0%	6	24%	10	40%	11	44%	6	24%	11	44%	
	3	25	100%	19	76%	11	44%	6	24%	4	16%	1	4%	
Physician score	**0**	0	0%	0	0%	0	0%	2	8%	5	20%	9	36%	**< 0.001 HS**
	1	0	0%	0	0%	4	16%	4	16%	5	20%	5	20%	
	2	0	0%	5	20%	7	28%	4	16%	7	28%	8	32%	
	3	25	100%	20	80%	14	56%	15	60%	8	32%	3	12%	
Total	**No Resp.**	25	100%	24	96%	13	52%	9	36%	2	8%	0	0%	**< 0.001 HS**
	Response	0	0%	1	4%	12	48%	16	64%	22	88%	20	80%	
	Remission	0	0%	0	0%	0	0%	0	0%	1	4%	5	20%	

HS: p-value < 0.001 is considered highly significant.
Table 4: comparison between Mayo score follow up in group I**.**

Variables	Group II	Baseline (N = 25)		3 weeks (N = 25)		6 weeks (N = 25)		9 weeks (N = 25)		18 weeks (N = 25)		24 weeks (N = 25)		p-value
Stool frequency	0	0	0%	0	0%	0	0%	4	16%	12	48%	19	76%	< 0.001 HS
	1	0	0%	0	0%	6	24%	8	32%	11	44%	5	20%	
	2	0	0%	7	28%	11	44%	10	40%	1	4%	1	4%	
	3	25	100%	18	72%	8	32%	3	12%	1	4%	0	0%	
Rectal Bleeding	0	0	0%	0	0%	0	0%	4	16%	10	40%	16	64%	< 0.001 HS
	1	0	0%	0	0%	5	20%	8	32%	8	32%	7	28%	
	2	0	0%	6	24%	10	40%	10	40%	7	28%	2	8%	
	3	25	100%	19	76%	10	40%	3	12%	0	0%	0	0%	
Mucosal app. At endoscope	0	0	0%	0	0%	0	0%	4	16%	12	48%	17	68%	< 0.001 HS
	1	0	0%	0	0%	7	28%	9	36%	11	44%	6	24%	
	2	0	0%	9	36%	10	40%	10	40%	1	4%	2	8%	
	3	25	100%	16	64%	8	32%	2	8%	1	4%	0	0%	
Physician score	0	0	0%	0	0%	0	0%	4	16%	9	36%	19	76%	< 0.001 HS
	1	0	0%	0	0%	6	24%	8	32%	8	32%	2	8%	
	2	0	0%	7	28%	11	44%	9	36%	7	28%	4	16%	
	3	25	100%	18	72%	8	32%	4	16%	1	4%	0	0%	
Total	No Resp.	25	100%	20	80%	7	28%	1	4%	0	0%	0	0%	< 0.001 HS
	Response	0	0%	5	20%	18	72%	23	92%	15	60%	7	28%	
	Remission	0	0%	0	0%	0	0%	1	4%	10	40%	18	72%	

HS: p-value < 0.001 is considered highly significant.
Table 5: comparison between Mayo score follow up in group II.

DISCUSSION

Fecal microbiota transplantation seems beneficial and safe for treatment of active UC based on the results of this study. As regard patients preparation we use bowel lavage with poly ethylene glycol and we did not use antibiotics before FMT as done by the four Randomized Clinical Trials (RCT) Paramsothy[9] et al, Rossen[10] et al , Moayyedi[11] et al and Costello[7] et al and other studies used antibiotics before FMT include Wei et al 12 who used Vancomycin 500 mg bd 3 days before FMT ,Ishikawa[13] et al who used Amoxicillin (1500mg/d),and metronidazole (750 mg/d) and Angelberger[14] et al who used Metronidazole 5-10 days before FMT.

Although the concept of adjuvant interventions, such as bowel lavage or pretreatment antibiotics, to decrease the bacterial burden and enable healthy microbial engraftment in the host has been speculated, it may also interfere with the function of the new microbiota.[15]
In our study we use of multiple donors (8-10) who un related to patients as done by Paramsothy et al 9 who used (3-7) donors and Costello et al who used (3-4) donors un related to patients on both studies.Un like Moayyedi[11] et al and Rossen[10] et al who used single donor for fecal microbiota transplantation infusion.

It was initially considered that related donors might lead to a better tolerance of FMT. However, the relatives of IBD patients have been recently demonstrated to possibly have themselves gut dysbiosis.[16] Multi donor fecal microbiota transplantation infusions were utilized in our study, both to ensure an adequate supply of infusions for fecal microbiota transplantation and to minimize the possibility of patients receiving only therapeutically ineffective donor stool.

In our study the amount of stool was (50 -100) gm. For each fecal microbiota transplantation with total amount reaching (200-400) gm at the end of study. This amount of stool was similar to Rossen[10] et al who used 120 gm of stool per week and Costello[7] et al who used 100gm of stool, per week, and disagree with paramsothy[9] et al who used the most intensive amount of stool who used (187.5) gm of stool per week for 8 weeks and moayyedi[11] et al who used amount of (8.3) gm of stool along the study.

In our study we use frozen donor stool from de-identified, unrelated healthy donors as done by Paramsothy9 et al and Costello7 et al who used the same method of processing. Other studies including Rossen[10] et al and moayeddi[11] et al who used fresh stool from single donor, Stool processed aerobically in our study as done by Moayyedi[11] et al, Paramsothy[9] et al and Rossen[10] et al un like Costello[7] et al the only study in which donors stool processed anaerobically without significant differences between studies, so it seems that neither

anaerobic vs aerobic stool preparation, nor fresh or frozen stool, significantly influences the efficacy of FMT.[17]

In our study we used colonoscopy as a route for delivery of fecal microbiota as done by Paramsothy9 et al and Costello7 et al who used colonoscopy for

microbiota transplantation, other studies using different routes were done by Moayyedi[11] et al who used retention enema and Rossen10 et al who used naso duodenal tube as a route of delivery of fecal microbioa.

In our study we use of colonoscopy to ensure that large quantity of stool delivered and to ensure that microbiota reaching the ileum and right colon, other studies used retention enemas explained that enemas are less expensive and safer to administer and more practical than colonoscopy.[11]

As to the administration route, in agreement with studies who used colonoscopy reported a possible increased benefit by using the lower route of administration in subgroup analyses, it has been speculated that the upper gastrointestinal route could interfere with the activity of some FMT components before they reach the colon (since gastric acid can damage Bacteroidetes), However, many bacteria belonging to the Firmicutes phylum require an upper GI tract transit in order to be activated, supporting a possible advantage of the upper route.[18]

In our study the duration of FMT was 9 weeks of transplantation(colonoscopy was done and FMT was done at 0,3,6,9 weeks of study) and follow up was done up to the 24th week of study, Similar duration was used by paramsothy[9] et al who had the duration of 8 week of transplantation and Moayyedi[11] et al demonstrated efficacy of FMT over placebo for 7 weeks, other studies used short duration include Rossen[10] et al demonstrated efficacy of FMT over placebo for 6 weeks and Costello[7] et al who used the shortest duration of 3- dose, 1-week of transfusion. The duration and intensity of faecal microbiota transplantation therapy might need to be individualized treatment once a week could be effective in some patients whereas more intensive therapy might be needed in others.

Both groups start with anemia HB (9.6) in group I and (9.4) in group II then improvement start to develop by the third week HB (9.8) on both groups and continue along the 6th week, the 9th week and the18th week, By the week 24 improvement in HB is more significant in group II HB (12.4) compared to (11.9) in group I with statistically significant difference between both groups P value (0.027).

Both groups start with leucocytic count (8.4) in group I and (8.3) in group II with no statistically significant difference between both groups II then improvement start to develop by the third week on both groups and continue along the 6th week, the 9th week and the18th week, By the week 24 reduction in leucocytic count is more significant in group II HB (5.8) compared to (6.2) in group I with statistically significant difference between both groups P value (0.008).

Patients of both groups start with high ESR level (35.3) in group I and (33.8) in group II then reduction in ESR achieved on both groups along

the study, By the 24th week ESR become normal on both groups (8.2) in group I and (7.5) in group II.

Patients of both groups start with high CRP level (29.8) in group I and (30.3) in group II then reduction in ESR achieved on both groups along the study, By the 24th week CRP become normal on both groups (3) in group I and (2,7) in group II. The clinical response is defined as reduction in mayo score equal or less than three points from base line score. The remission is defined as a resolution of clinical symptoms, including cessation of rectal bleeding and improvement in bowel habits (total mayo score equal or less than 2).

At the start of study both groups were in exacerbation (mayo score was 12). At the third week both groups start to improve with where 4% (1/25) of patients of group I achieved clinical response and 20% (5/25) of patients of group II achieved clinical response and no remission achieved on both groups with no statistically significant difference between both groups. By the 6th week of study more patients of both groups achieved clinical response where 72%(18/25) of patients of group II become responsive to treatment and 48%(12/25) of patients of group I responsive to treatment as regard reduction in mayo score to (9.4) in group I compared to (8.4) reduction in mayo score in group II with no statistically significant difference between both groups. By the 9th week 92% (23/25) of patients of group II achieved clinical response compared to 64%(16/25) and one patient of group II (4%) achieved clinical remission (reduction mayo score to equal or less than two) with no remission achieved in group I. By the 18th week of study 40% (10/25) of patients of group II achieved clinical remission and only one patient of group I achieved clinical remission. At the end of the study by the 24th week 72% (18/25) of patients of group II achieved clinical remission and only 20%(5/25) of patients of group I achieved clinical remission.

The end result of this study agree with paramsothy[9] et al in which remission induction achieved in 44%(18/41) and Costello[7] et al where is 50% (19/38) achieved clinical remission, And disagree with moayddei[11] et al, Angelberger[14] et al and nishida[19] et al in which no clinical remission achieved in all patients and Rossen[10] et al in which 30% only of patients achieved clinical remission.

CONCLUSION

FMT provides a promising new therapy for UC with Successful FMT associated with decreased activity of the disease and more well designed studies on large scale of patients and long-term follow-up are necessary to confirm the effects of FMT.

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