Annals of Clinical and Medical Case Reports

ISSN 2639-8109

Research Article

Preliminary Results of Fecal Microbiota Transplantation in Diarrhea-Predominant Irritable Bowel Syndrome: Case Series on 12 Patients

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Volume 4 Issue 1- 2020

Received Date: 07 Apr 2020

Accepted Date: 14 May 2020

Published Date: 19 May 2020

2. Keywords:

Fecal Microbiota Transplantation; Irritable Bowel Syndrome; Diarrhea

1. Abstract

1.1. Background and Aims: Irritable Bowel Syndrome (IBS) is associated with intestinal dysbiosis and it has been suggested Fecal Microbiota Transplantation (FMT) has a positive effect on the condition. In this preliminary study, we recruited 12 IBS patients with moderate to severe diarrhea (IBS-D) and assessed the clinical outcomes of single FMT.

1.2. Materials and Methods: Patients underwent a clinical assessment to determine compliance, symptoms, and safety at baseline and at 1, 3, and 6 months after FMT. At these visits, patients submitted self-reports on stool form/frequency and completed IBS severity score (IBS-SSS), Birmingham IBS symptom score, and submitted IBS-Quality of Life (IBS-QOL) questionnaires. Fecal samples were collected from patients before and after FMT.

1.3. Results: Mean age of the 12 study subjects was 54.2 ±12.5 years and 58% (7/12) were men, and the predominant complaint of all the participated patients was diarrhea. Baseline of mean IBS-SSS and mean total Birmingham score was 261 and 42.2. Ten patients showed significant improvement compared to baseline IBS severity score, from a mean 259 to 127.5 points at 3 months after FMT ($p<0.05$). According to the Birmingham IBS symptom scale, total scores including abdominal pain and diarrhea were significantly reduced at 1 and 3 months after FMT ($p<0.05$).

1.4. Conclusion: In this preliminary study, FMT was found to provide significant IBS-D symptom relief over 6 months.

3. Abbreviations: IBS: Irritable Bowel Syndrome; GI: Gastrointestinal; FMT: Fecal Microbiota Transplantation; CID; Clostridium Difficile Infection; IBS-D: Diarrhea-Predominant IBS; IBS-C: Constipation-Predominant; IBS-M: Mixed IBS; IBS-SSS: IBS Severity Symptom Scale; HIV: Human Immunodeficiency Virus; HBV: Hepatitis B; HCV: Hepatitis C; HAV: Hepatitis A; IBS-QOL: IBS-Quality of Life

4. Introduction

Irritable Bowel Syndrome (IBS) is the most commonly diagnosed gastrointestinal (GI) condition and affects up to 10-15% of the adult population [1]. IBS has a serious impact on quality of life, productivity, and social functioning and places a high cost burden on health care systems [2]. Unfortunately, despite advances in our understanding of the pathophysiology of IBS, no treatment is available that specifically targets IBS though an algorithm has been constructed to guide practicing clinicians who encounter this disorder [3]. Current evidence suggests that microbiota of the GI tract could be a significant factor in the etiology of IBS [4], and changes in the intestinal environment have been suggested to induce compositional imbalance in gut microbiota, a phenomenon termed 'dysbiosis', which is associated with IBS [5].

There is a growing interest in Fecal Microbiota Transplantation (FMT) therapy for various GI disorders, and in non-GI disorders including Parkinson's disease, fibromyalgia, and metabolic syndromes associated with altered intestinal microbiota [6, 7]. In particular, FMT has been hugely successful for the treatment of Clostridium Difficile Infection (CDI) [8] and has a much higher cure rate than antibiotic treatment [9]. Furthermore, studies indicate FMT restores intestinal microbial balance [10, 11].

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Citation: Park Jin-Seok, Preliminary Results of Fecal Microbiota Transplantation in Diarrhea-Predominant Irritable Bowel Syndrome: Case Series on 12 Patients. Annals of Clinical and Medical Case Reports. 2020; 4(1): 1-6.

In the regards of the effect of FMT for IBS, few studies have addressed the use of FMT for IBS and almost all of studies were case reports or case series [8, 12]. In the results of these studies, FMT provided better symptom relief in diarrhea-predominant IBS (IBS-D) than in constipation-predominant (IBS-C) or mixed IBS (IBS-M) because IBS-D exhibits higher microbiota diversity than those of IBS-C which is more susceptible condition for FMT. However, there is no report conducting with only patients with IBS-D. Therefore, the effect of FMT for IBS-D is still ambiguous.

Therefore, we conducted pilot study to evaluate the efficacy and safety of FMT for refractory IBS-D patients using a questionnaire approach.

5. Materials and Methods

5.1. Participants

This study was conducted using a prospective, single-center, pilot design. Patients were recruited at Inha University Hospital. Informed consent was obtained from all study participants and all had a diagnosis of IBS-D according to Rome IV criteria [13]. Patients had moderate-to-severe disease activity based on the IBS severity symptom scale (IBS-SSS), that is, a score of > 175 points. Refractory IBS was defined as failure to respond to currently available IBS treatments, which included dietary changes and treatment with antibiotics or probiotics, antidepressants, or psychotherapies over a period of 6 months [14]. The treatment method and side effects of FMT were explained to patients prior to treatment commencement. Patients underwent FMT between January 2015 and August 2016.

Inclusion criteria were as follows: i) Experience of abdominal pain at least 1 day a week on average during the preceding 3 months; ii) Association with ≥2 of the following; defecation, change in stool frequency, or a change in stool appearance; iii) >25% of bowel movements of Bristol Stool Scale Types 6-7 or <25% of Types 1-2; and iv) normal colonoscopy performed within 1 year of FMT for patients ≥40 years old or if a patient passed bloody stools.

The study exclusion criteria were: i) coexistence of other severe disease, including other intestinal diseases including CDI, diabetes, or cancer, or follow-up of less than 3 months; ii) a positive screening result for Human Immunodeficiency Virus (HIV), Hepatitis B (HBV), or Hepatitis C (HCV) antibody; or iii) surgical intervention in the GI region excepting appendectomy, hernia repair, cholecystectomy, and gynecological and urological procedures.

5.2. Recipient Preparation

The day before the procedure, recipients received a standard split-dose polyethylene glycol–based bowel preparation in anticipation of colonoscopy. Patients did not eat for 8 hours before FMT, and at least a week before FMT, all conventional diarrhea treatment was stopped. During the study period, all patients were requested to maintain previous diet, exercise, and lifestyle. All patients were fully informed of the advantages and potential adverse events of standardized FMT.

5.3. Stool Donor Screening

Stools were donated by family members, friends, or a healthy donor. Before FMT, we asked members of patients' families to select a stool donor. If a suitable stool donor was not available, we selected an unrelated healthy volunteer as a donor. Potential donors were scrutinized and screened to minimize the risk of transmitting infectious diseases. Donor stool testing included an ova and parasite exam, testing for the presence of C. difficile toxin, Rotavirus antigen, and Giardia antigen, and stool culture for Salmonella, Shigella, and Campylobacter species. Donor blood testing included complete blood count, blood chemistry testing, amoebic antibody, hepatitis A (HAV), HBV, HCV, HIV Ag/Ab, and for venereal diseases.

5.4. Preparation of Fecal Suspension

FMT preparation involved mixing 100 g of fresh stool in a blender with 500 mL of 0.9% sterile saline to a smooth consistency. The suspension was then filtered through gauze pads or strainer to remove large particles, poured into an aseptic bottle, and administered within 1 hour.

5.5. Route of Administration

An experienced endoscopist performed ileocolonoscopy. Donor stool suspension of 300 ml was injected into the cecum through the biopsy channel of colonoscope. None of the patients had any contraindication for fecal transplantation. A biopsy was performed when considered appropriate by an experienced endoscopist. Patients were instructed to contact our hospital if they have any symptom exacerbation or relapse of diarrhea after transplantation. In addition, patients were asked to visit hospital at scheduled times 1, 3, and 6 months after FMT. If a patient failed to attend a scheduled visit, he/she was contacted by telephone for up to 24 weeks after FMT.

5.6. Outcome Measurements

Twelve patients visited our clinic for the assessment of compliance, symptoms, and safety at baseline and at 1, 3, and 6 months after FMT (Figure 1). At these visits, patients submitted self-administered questionnaires were used to determine stool forms/frequencies, and IBS-SSS and Birmingham IBS symptom scores. Fecal samples were collected from patients before and after FMT.

The primary end points were IBS-SSS scores before and 1, 3, and 6 months after FMT. This scale evaluates the intensities of IBS symptoms such as abdominal pain, distension, stool frequency, and stool consistency and the interference daily life during a 10-day period. The IBS-SSS involves assessing each of these 5 items using a

visual analog scale from 0 to 100 and summing the results [15]. The second primary end point was stool consistency was assessed using the Bristol Stool Form Scale. The third was safety end points which were adverse events during FMT and follow-up, for example, abdominal pain, diarrhea, nausea, vomiting, bloating, and flatulence. The secondary end points were Birmingham IBS symptom scores before and 1, 3, 6 months after FMT. The Birmingham IBS symptom score questionnaire is a self-completed questionnaire that contains 11 questions that address the frequency of IBS-related symptoms. Each question is rated using a 6-point Likert scale ranging from 0 = none of the time to 5 = all of the time [16]. The second is IBS-Quality of Life (IBS-QOL) Questionnaire Scores which is a 34-item instrument developed and validated for the measurement of patient health-related quality of life [17]. The third is numbers of doctor appointments or emergency room visits made for the treatment of uncontrolled IBS symptoms, and the forth is number of new medications initiated for the treatment of uncontrolled IBS symptoms. Data were collected using daily patient diaries and by telephone follow-up.

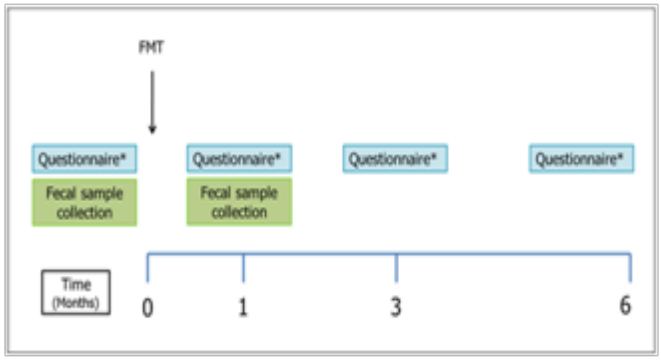

Figure 1: A Flow diagram illustrating the study design

Table 1: General characteristics of 12 patients

Variables (n=12)	No. of cases	(%)
Age (years)		
Mean ± SD, range	54.2 ± 12.5	33-70
Gender, n (%)		
Male	7	-58.3
Female	5	-41.7
BMI		
Mean ± SD, range	24.5 ± 4.1	17.3-30
Predominant bowel habit, n (%)		
Diarrhea	12	-100
Constipation/Alternating/Unsubtype	0	0
Smoking, N (%)		
Non-smoker	5	-41.7
Former smoker	5	-41.7
Smoker	2	-16.7
Duration of IBS symptoms, n (%)		
1-5 years	9	-75
>5 years	3	-25
IBS-SSS (Max score 500)	Mean	SD
	250	-79.2
IBS symptoms (Birmingham Score Max score 100)	Mean	SD
Constipation	0.15	0.5
Diarrhea	38.2	13.2
Pain	49.2	26.2
Total	57.9	10.1
Stool frequency (Stools per day)	Mean	SD
	5.8	-0.9
Stool consistency (from Bristol stool form)	Mean	SD
	5.5	-0.66
Concomitant drug, n (%)		
Probiotics	11	-91.7
Antispasmodic	10	-83.3
Antidiarrheal	7	-58.3
Anti-depressants	4	-33.3
Severe complication & expire, n (%)	0	0

Abbreviations: BMI; Body Mass Index, IBS; Irritable Bowel Syndrome, IBS-SSS; IBS-Severity Symptom Scale

5.7. Statistics

Continuous data are presented as means ± SDs, and categorical data as n (%). Statistical analyses of changes in total scores and subscores versus baseline were performed using the paired t-test or Wilcoxon's signed-rank test. The analysis was performed using SPSS software (version 19.0; SPSS Inc., Chicago, IL), and p values of <0.05 were considered significant.

5.8. Ethics

Written informed consent, which included laboratory screening requirements, was obtained from all 13 study subjects prior to study commencement, and the study was approved by the Institutional Review Board of Inha University Hospital (2016-04-009).

6. Results

6.1. Patients' Characteristics

During the study period, 13 patients with IBS-D were enrolled. However, one patient was lost to follow-up after FMT, did not undergo 4-week evaluation, and was excluded from the results and the analysis. Consequently, 12 patients completed pre- and post-FMT evaluations. Patient characteristics are shown in Table 1. Mean age of the 12 study subjects was 54±12.5 years and 58% were men. Most of the study subjects complained of diarrhea and 16.7% were current smokers. Symptom durations were <5 years in 75% and >5 in 25%. Mean IBS-SSS score was 250±79.1 and mean Birmingham IBS symptom score was 57.9±10.1. Mean stool frequency was 5.8±0.9 times per day, and mean stool consistency according to the Bristol stool form scale was 5.5. No patient experienced a mortality-associated complication.

6.2. The outcomes of FMT on IBS

A comparison between the pre- and post-FMT IBS-SSS of all study subjects demonstrated significant reductions compare baseline (250.0±79.2) to weeks 4 (138.3±100.7) ($p<0.05$), 12 (125.8 ±88.7) ($p<0.01$), and 24 (124.2 ±91.8) ($p<0.01$) (Figure 2). Mean stool consistency scores tended to improve after FMT; pre-FMT (5.5±0.7), week 4 (4.3±1.0), week 12 (4.2±0.9), and week 24 (4.2±0.9) ($p<0.001$).

There were no severe nor obvious adverse events after the endoscopic procedure, FMT, or during the 6-month follow-up period. The most common symptom was flatulence (33%, 4/12), but this disappeared within the first 4 weeks. Three patients experienced abdominal bloating and one patient borborygmus, but all recovered within 4 weeks. One patient, whose symptoms were well controlled without adding new drugs, visited the emergency room with abdominal pain 5 months after FMT. Abdominal computed tomography and blood tests showed non-specific findings. Symptoms improved after conservative treatment at home and no symptom recurrence subsequently occurred.

FMT also reduced the severity of diarrhea. Mean stool frequencies decreased from 5.8 per day pre-FMT to 3.5 per day at 4 weeks, 3.2 at 12 weeks, 2.9 at week 24 post-FMT ($p<0.001$). Mean Birmingham IBS symptom scores were also significantly decreased at week 4 (13.4±6.2), week 12 (13.8±7.2), and week 24 (14.7±8.7) as compared with baseline score (23.2± 5.6) ($p<0.01$) (Figure 3). According to IBS-QOL scores (Figure 4), IBS-D patients showed greater impairments on dysphoria, body image, food avoidance, and relationship subscales than the rest of subscales before FMT treatment. After 4, 12, and 24 weeks, the mean scores of IBS-QOL total revealed significant decreased over time compared to the baseline (Table 2).

There were no unplanned doctor appointments for uncontrolled symptoms of IBS. No patients started new medication for the treatment of uncontrolled IBS symptoms.

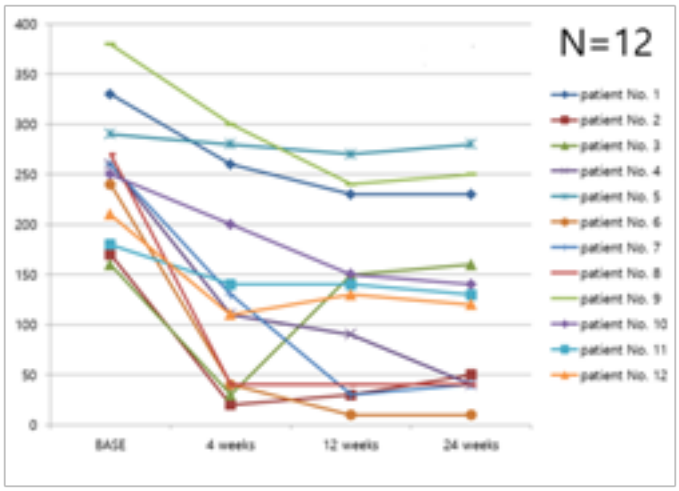

Figure 2: Changes of pre-FMT and post-FMT IBS-SSS over 24 weeks

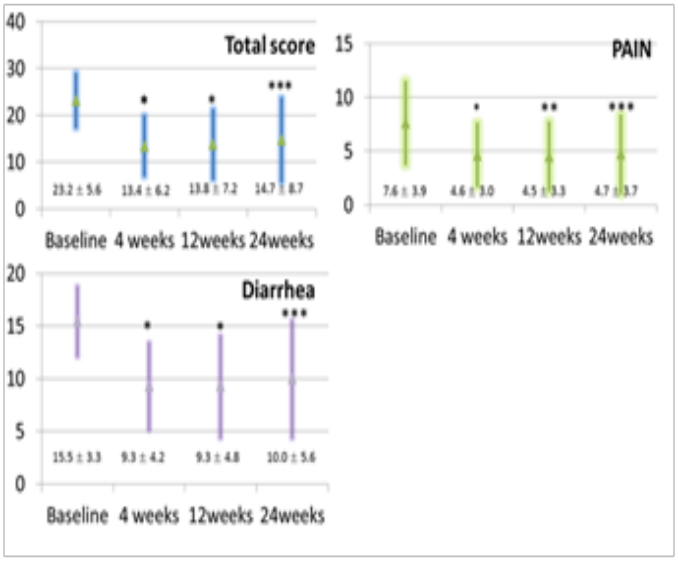

Figure 3: Changes of pre-FMT and post-FMT Birmingham IBS symptom scale over 24 weeks

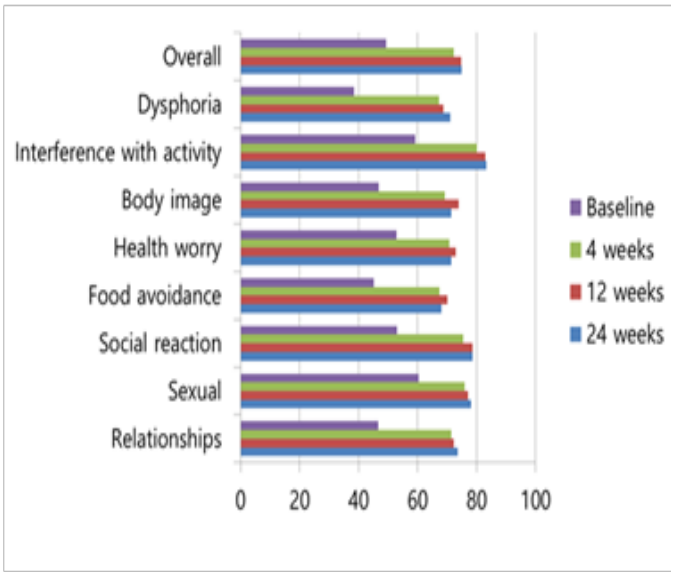

Figure 4: Changes of pre-FMT and post-FMT IBS-QOL subscale score

7. Discussion

In current study, we found that FMT is an effective treatment for refractory IBS-D. Stool consistencies were significantly improved compared to 24 weeks post-FMT, and IBS-SSS, Birmingham IBS symptom, and IBS-QOL scores revealed significant improvements at 1, 3, and 6 months ($p<0.01$) after FMT.

FMT is in generally considered to be safe and its side effects have been reported to be mild, self-limiting, and GI in nature [18]. However, the safety of FMT has been mainly studied in the context of CDI, and little information is available regarding the safety of FMT for the treatment of functional GI disease [19, 20]. Recently, in a long-term follow-up study of 13 patients who underwent FMT for refractory IBS, only 1 patient experienced a transient increase in flatus. Over an average follow-up of 11 months, there were no long-term side effects, and none of the patients developed any new disease [20]. Similar to our present study, there were no severe adverse events after FMT but only minor symptoms of abdominal pain, bloating (2/12), flatulence (3/12), and borborygmus (1/12) were recorded during follow-up, and even these minor symptoms diminished shortly after FMT. Our results indicate that FMT may be considered a safe treatment for IBS-D and is well tolerated.

The effect of FMT on IBS-D symptom relief has not been maintained for a long time and 2 patients of IBS-D symptoms regressed to their pre-treatment states by 1 month after FMT and complained of diarrhea and abdominal pain. Similar result was reported in a Danish study [19] of 6-month follow-up study on 52 adult patients. IBS-D symptom relief by FMT was peaked at 1 month post-FMT and remained at this level after 3 and 6 months post-FMT. However, IBS-SSS and IBS-QOL scores did not improve significantly after 1-month post-FMT. Based on these results, multiple sessions

of FMT might be needed to enhance the efficacy of FMT on IBS-D since transplanted intestinal bacteria may not permanently colonize the intestine of IBS-D patients. However, multiple sessions of FMT have not been studied yet and only a trial of multiple FMTs has been reported that is effective in the treatment of recurrent CDI [21, 22]. Therefore, well-designed clinical trials are required to establish the effectiveness of multiple session of FMT on IBS-D.

Several limitations of the present study require consideration. First, though a prospective study, it was performed only in 12 patients, which could have resulted in selection bias. Second, no placebo control group was included for comparison. Third, follow-up was conducted for only 6 months, and thus, we suggest further long-term study be conducted. In spite of small number of patients, the marked clinical improvements observed after FMT warrant further investigation to clarify the contribution made by fecal microbiota to the etiology of diarrhea. Fourth, clinical improvements were based on patient`s subjective self-reports and no objective indicators such as measures of microbiota diversity were included. We chose colonoscopy as the method of FMT administration, because in a previous meta-analysis, a forest plot of randomized controlled trials of FMT in IBS generally showed better results for this route or nasogastric tube administration than for oral FMT capsule administration [23]. However, no study has yet directly compared the effects of FMT capsule and endoscopic administration.

We conclude that FMT may improve the symptoms of IBS-D until 6 months after FMT. However, the effects of FMT seem to decrease over time, which raises consideration of booster administrations.

Table 2: Changes of pre-FMT and post-FMT IBS-QOL score

Visit	IBS-QOL score								
(n=12)	Total	Dysphoria	Interference With Activity	Body Image	Health Worry	Food Avoidance	Social Reaction	Sexual	Relationship
Week 0	49.3	38.5 (19.00)	59.2	46.9 (17.58)	52.8 (13.91)	45.1 (17.93)	53.1 (16.96)	60.4 (14.91)	46.6
	-16.44		-17.13						-19.26
Week 4	72.3	67.2 (25.58)	80.1	69.3 (23.15)	70.8 (18.63)	67.4 (16.07)	75.5 (23.61)	76.0 (16.39)	71.5
	-20.27		-16.92						-20.86
Week 12	74.8	68.8 (23.00)	83	74.0 (21.95)	72.9 (19.17)	70.1 (16.84)	78.6 (20.89)	77.1 (12.87)	72.2
	-17.94		-13.72						-18.23
Week 24	74.9	71.1 (24.39)	83.3	71.4 (21.89)	71.5 (17.21)	68.1 (15.82)	78.6 (21.89)	78.1 (13.19)	73.6
	-18.61		-15.25						-18.75
Change from week 0 to 4	74.9	28.6 (18.88)*	20.8	22.4 (16.95)**	18.1 (14.14)***	22.2 (14.79)***	22.4 (19.12)***	15.6 (15.19)	25
	-18.61		(13.44)*						(19.13)**
Change from week 0 to 12	23	30.2	23.8	27.1 (21.38)***	20.1 (18.62)***	25.0 (19.46)**	25.5 (21.06)**	16.7 (15.39)	25.7
	(14.81)*	(22.31)**	(16.00)*						(21.16)**
Change from week 0 to 24	25.6	32.6	24.1	24.5	18.7	22.9	25.5	17.7	27.1
	(19.67)**	(25.55)**	(20.15)***	(24.05)***	(17.09)***	(18.84)**	(21.40)***	(14.56)**	(21.65)**

Abbreviations: IBS; Irritable Bowel Syndrome, IBS-QOL; IBS-Quality of Life
IBS-QOL score, *: p<0.001, **: p=0.001, ***: p<0.01

8. Acknowledgements

This research was supported by the Bio & Medical Technology Development Program of the National Research Foundation (NRF) & funded by the Korean government (MSIT) (2019069613).

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