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Original Article

Efficacy of Fecal Microbiota Transplant in Patients with Moderate or Severe Irritable Bowel Syndrome in India

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ABSTRACT

Background and Aim: To study effect of FMT in patients with moderate or severe IBS.
Methods: Patients with IBS for more than one year were offered three sessions of colonoscopicFMT in addition to standard of care. Severity of disease, psychological distress and QOL were assessed by IBS-SSS, HAM-D, HAM-A and WHO-QOL scores.
Results: Ten patients with IBS (IBS-D 5, IBS-C 4 and IBS-M 1) were studied. Median IBS-SSS reduced from 313.5 (SD ± 66.8) at baseline to 163 (SD ± 84.5) at 1 week (p = 0.0005), 216 (SD ± 79.3) at 2 weeks (p = 0.003), 201(SD ± 86.6) at 4 weeks (p = 0.005) and 262 (SD ± 69.4) at 8 weeks. Median IBS-SSS at 12 weeks and 24 weeks was not significantly different from baseline. Reduction of IBS-SSS severity was seen in 8 (80%) patients at one week, 6(60%) at 2 and 4 weeks, 3(30%) at 8 weeks and 1(10%) at 12 and 24 weeks. weeks. Of four patients with depression, there was improvement in two patients at 2 and 4 weeks and one at 8 weeks. Quality of life improved in four patients at 2, 4 and 8 weeks, two patients at 12 weeks and one at 24 weeks. Three patients reported marked improvement of symptoms at 12 months along with change in stool odor to donor type.
Conclusion: FMT results in short-term improvement in global symptoms of IBS, psychological distress and QOL. Repeat sessions of FMT did not accrue additional benefit.

KEYWORDS: Irritable Bowel Syndrome, Fecal Microbiota Transplant, Colonoscopic FMT.

Introduction

Of all the functional gastrointestinal disorders, Irritable Bowel Syndrome (IBS) is the most common with a worldwide prevalence of 12%[1]. Defined by Rome-IV criteria, IBS is classified into four subtypes: IBS with predominant constipation (IBS-C), predominant diarrhea (IBS-D), mixed bowel habits (IBS-M) or unsubtyped(IBS-U)[2]. The pathophysiology of IBS is multifactorial with influence of infections, diet, gut

microbiome and a complex brain-gut interaction, thus presenting considerable difficulty in treatment. Fecal Microbiota Transplantation (FMT) is the term used to describe the infusion of a fecal suspension from a healthy individual into the gastrointestinal tract of another individual. FMT is now an established indication for refractory Clostridium difficile infection[3]. A recent meta-analysis that included four randomized control trials concluded that FMT may be more effective than placebo in inducing clinical remission and clinical response in patients with Ulcerative Colitis[4]. We carried out the first successful FMT for Ulcerative Colitis in India in 2014[5]. Role of FMT in disorders like Irritable Bowel Syndrome (IBS), Crohn's disease, Alcoholic liver disease, Parkinson's, Autism, Metabolic syndrome and Idiopathic Thrombocytopenic Purpura is under investigation[6]. Up to 30% of patients with IBS are post-infectious and dysbiosis is now accepted as a predominant factor in the pathophysiology of IBS with relative abundance of proinflammatory bacteria like Enterobacteriaceae and a reduction in Lactobacillus and Bifidobacterium[7]. New strategies of treatment of IBS are focusing on gut bacteria modulation, of which FMT features prominently[8]. We carried out an open label single arm cohort study on FMT in patients with moderate or severe IBS.

Methods

Patients with IBS of more than one-year duration, who remained symptomatic despite medical therapy, were offered FMT in addition to standard of care. The diagnosis of IBS was based on Rome IV criteria and sub-classification of IBS was based on the Bristol stool type[9]. The severity of disease was assessed by IBS-Symptom Severity Score (IBS-SSS), where a score of 75 to 174 indicated mild symptoms, 175 to 299 moderate IBS and score of 300 and above severe IBS[10]. Pain abdomen was considered to be significant if the pain score was above 50 in the IBS-SSS. The associated psychological distress and quality of life were be assessed by Hamilton Rating Scale for Depression (HAM-D), Hamilton Rating Scale for Anxiety (HAM-A) and World Health Organization Quality of Life (WHO-QOL) scales[11,12,13]. HAM-Dscore of 8 to 13 was indicative of mild depression, 14 to 18 moderate, 19 to 22 severe and 23 or higher,very severe depression. HAM-A score of 17 or less was suggestive of mild anxiety, 18 to 24 moderate and 25 to 30 severe symptoms. Patients with pregnancy, severe anemia, active gastrointestinal infection, antibiotic or probiotic use over last 30 days, chronic kidney disease, cirrhosis of liver, cardiac failure, malignancy, uncontrolled diabetes mellitus, and uncontrolled thyroid disorderswere excluded. Recipient evaluation included exclusion of other diseases with complete blood count, C-reactive protein, serum Chromogranin A & B, upper gastrointestinal endoscopy and duodenal biopsy, colonoscopy with random biopsy, contrast enhanced CT scan of abdomen, Hydrogen breath tests for lactose intolerance and Small Intestinal Bacterial Overgrowth (SIBO). Also, stool was tested for ova and cysts, culture, Calprotectin, modified Ziehl Nielson stain, Cryptosporidium antigen and Clostridium difficile toxin A and B assay. Donor screening and testing was carried out as per European consensus on FMT in clinical practice to rule out communicable diseases, gastrointestinal, rheumatic, allergic and metabolic disorders[14]. Stool donors who received antibiotics within the preceding 3 months were excluded. 200 gram of donor stool, collected with-in 6 hours of FMT, was blended, filtered and drawn up into a total of 7 syringes of 50 ml each and instilled following informed consent, into the recipient colon at colonoscopy. Thereafter, 2 sessions of FMT were performed fortnightly with instillation of 50 gram of stool from same donor in 50 ml of water into the left colonat flexible sigmoidoscopy. The IBS-SSS was assessed at 1, 2, 4, 8,12 and 24 weeks and HAM-D, HAM-A and WHO-QOL were assessed at 2, 4, 8, 12 and 24 weeks following FMT. The pre-intervention medication remained unchanged for six months after FMT, following which lowest dose was taken to maintain remission. A follow-up questionnaire was used at one year for assessment of symptoms, requirement of medication and to determine the over-all experience of patients following FMT.

Outcome measures

The primary outcome studied was improvement in global symptoms of IBS as defined by reduction in severity of IBS-SSS from severe to moderate/mild or moderate to

mild. Secondary outcomes included improvement in HAM-D and HAM-A and WHO-QOL. The parameters of responders and non-responders were compared in an attempt to identify factors that determined response. Relapse was defined as return of IBS-SSS to the pre-intervention severity in patients with response. Adverse events were monitored prospectively.

Statistical methods

Paired T Test was used to compare mean and standard deviation for IBS-SSS scores before and after FMT. Each entity was measured twice, resulting in pairs of observations as one tail and two tail. The age and duration of IBS among responders and non-responders was compared with Mann-Whitney U test. The Fisher Exact test was used to analyze the association of SIBO, lactose intolerance, anxiety and depression between responders and non-responders.

Results

Ten patients, median age 34 (range 18 to 70) years, including 8 males, were studied. The median duration of IBS was 10 (range 5 to 30) years, with five classified as IBS-D, four as IBS-C and one IBS-M. Significant pain abdomen with scores of above 50 in IBS-SSS was present in 5(50%). Three patients had associated lactose intolerance, one had SIBO and two had both lactose intolerance and SIBO (**Table 1**). Baseline median IBS-SSS was 360 (range 260 to 390) with moderate IBS in five and severe IBS in five patients. Six patients had depression at baseline with median HAM-D score of 8(range 0 17). Two patients had high HAM-A scores of 19 and 22 and both had mixed anxiety depression disorder. The median WHO-QOL overall score at baseline was 59 (range 44 to 87). The median age of stool donors was 33 years (range 25 to 72 years) with six males and three spousal donors. All patients completed the FMT protocol.

The trends of IBS-SSS over 24 weeks following FMT in the 10 patients are shown in **Figure 1**. Median IBS-SSS significantly improved at week 1, 2, 4, and 8 but not at week 12 and 24. Median IBS-SSS reduced from 313.5 (SD ± 66.8) at baseline to 163 (SD ± 84.5) at 1 week ($p = 0.0005$), 216 (SD ± 79.3) at 2 weeks ($p = 0.003$), 201(SD ± 86.6) at 4 weeks ($p = 0.005$) and 262 (SD ± 69.4) at 8 weeks. Median IBS-SSS at 12 weeks, 292 (SD ± 95), and 24 weeks, 294 (SD ± 95.1), was not significantly different from baseline ($p = 0.19$ and 0.21, respectively). Reduction of IBS-SSS by at least one grade

Table 1: Demography, type of IBS, co-morbidities, IBS-SSS, depression and anxiety scores at baseline in 10 patients.

Sl. No.	Age in years	Sex	Duration of IBS in years	Type of IBS	Pain abdo-menscore	SIBO	Lactose intolerance	Co-morbidities	Baseline scores			Medications
									IBS-SSS	HAM-D	HAM-A	
1	68	M	30	IBS-D	20	yes	yes	DM, HTN	260	0	2	Rif, Pro, Isp
2	38	M	17	IBS-D	80	yes	no	nil	390	0	0	Rif, Pro,Nor
3	36	M	7	IBS-D	75	no	no	nil	375	4	4	Rif, Pro, PPI, Cime, Chlor
4	28	M	7	IBS-D	20	no	no	nil	230	8	5	Rif, Pro
5	33	F	18	IBS-D	90	no	yes	Seizure disorder	390	14	6	Rif, Pro,Nor
6	17	F	9	IBS-C	90	yes	yes	nil	360	17	22	Peg, Pru, Chlor, Clin, Dicy
7	31	M	5	IBS-C	40	no	no	nil	240	13	6	Peg, Pru, Chlor
8	37	M	10	IBS-C	nil	no	yes	nil	280	13	15	Pro, Les, Peg
9	27	M	10	IBS-C	70	no	yes	nil	360	17	19	Pro, Rif, Peg
10	44	M	21	IBS-M	nil	no	no	Nil	250	2	3	Pro, Peg

SIBO: Small intestine bacterial overgrowth, DM: Diabetes Mellitus, HTN: hypertension, Rif: Rifaximin, Pro: Probiotics, Isp: Ispaghula, Nor: Nortryptilline, PPI: Proton pump inhibitor, Cime: Cimetropium, Chlor: Chlordiazepoxide, Peg: Polyethylene glycol, Pru: Prucalopride, Clin: Clinidium, Dicy: Dicyclomine, Les: Lesuride.

was noted in 8 of 10 (80%) patients at one week after FMT, 6 of 10(60%) at 2 and 4 weeks, 3(30%) at 8 weeks and 1(10%) at 12 and 24 weeks. The temporal profile of response to IBS-SSS and correlation with more than 50% improvement in bloating and bowel habits is shown in **Figure 2**. Of the five patients who had IBS-SSS pain score of more than 50 at baseline, greater than 50% reduction in pain abdomen was seen in four patients at 1,2 and 4 weeks, two at 8 weeks and none at 12 and 24 weeks.

Age of patients, duration of IBS, type and severity of IBS, associated SIBO or lactose intolerance and prevalence of depression or anxiety did not predict response at four weeks (**Table 2**). Repeat sessions of FMT by sigmoidoscopic instillation at two and four weeks had a positive impact on IBS-SSS in only one patient out of ten.

Of four patients with depression, there was improvement in grade of HAM-D score in two patients at 2 and 4 weeks, one patient at 8 weeks and none of the patients at 12 and 24 weeks. One of the two patients with mixed anxiety depression disorder showed improvement at 2 and 4 weeks only. All patients who had improvement in IBS-SSS showed improvement in HAM-D and HAM-A. Quality of life improved in four (40%) patients at 2, 4 and 8 weeks and two patients at 12 weeks and one at 24 weeks. Three of these four patients had shown clinical response to IBS-SSS while one showed improvement in WHO-QOL despite clinical non-response.

None of our patients reported significant adverse events following FMT. Two (20%) patients developed transient abdominal cramps and vomiting for 12 hours following FMT. One patient reported shifting in site of pain from left lower abdomen to central abdomen three months following FMT.

In response to a questionnaire at the end of one year, seven out of ten patients did not regret enrolling for the trial on FMT and said that they would not mind doing it again provided there was a better alternative to processing stool at home. Six of them said they would recommend FMT to others based on their own experience. Five patients reported change in odor of their stool to donor stool following FMT that lasted for about two months. Interestingly, three patients, all of whom had relapse following initial improvement, reported marked improvement of symptoms at 12 months. They reported

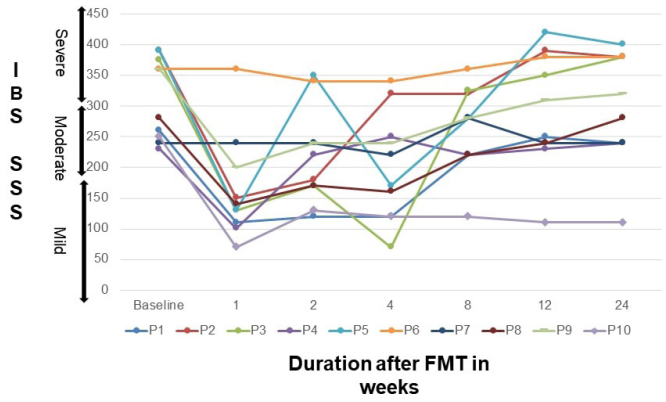

Figure 1: Trends in IBS-SSS over 24 weeks following FMT.

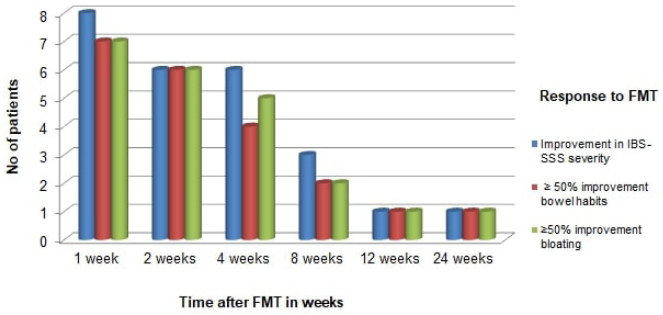

Figure 2: Waning response to reduction in IBS-SSS, improvement in bloating and bowel habits over 24 weeks after FMT.

that the odor of their stool changed to that of the donor at about nine to ten months post FMT with more than 50% reduction in their symptoms with two of them being off all medication.

Discussion

The results of our study, the first of its kind from India, are very similar to the few other open label studies on colonoscopic FMT for IBS. Cruz *et al*. from Germany reported transient improvement in nine patients with profound changes in the microbiome of patients with IBS-D[15]. Hong *et al*. from Korea reported improvement in IBS-SSS in 80% patients at one month in 12 patients, but the symptoms returned to baseline at 3 months[16]. In a meta-analysis of single arm trials by Myneedu *et al*, 59.5% (95% confidence interval (CI) 49.1–69.3) of IBS

Table 2: Comparison of responders and non-responders at 4 weeks after FMT.

Parameters	Responders (n=6)	Non-responders (n=4)	p-value		Statistical test applied
	Median (Range)	Median (Range)			
IBS-SSS	165 (70-260)	285 (220-340)	0.067		Mann-Whitney U test
Age (yrs.)	36.5 (27-68)	29.5 (17-38)	0.257		
Duration of IBS	14 (7-30)	8 (5-17)	0.114		
Parameters	**Responders (n=6)**	**Non-responders (n=4)**	**p-value (1-tail)**	**p-value (2-tail)**	**Statistical test applied**
Type of IBS : IBS-D	3	2	0.738	1.000	Fisher Exact test
: IBS-C	2	2			
: IBS-M	1	0			
Associated SIBO : Positive	1	2	0.333	0.500	
Associated lactose intolerance: Positive	4	1	0.262	0.524	
Associated Depression	2	2	0.548	1.000	
Associated Anxiety: Mild severity/Severe	4	3	0.667	1.000	
Associated Anxiety: Severe	1	1	0.667	1.000	
Mixed Anxiety Depression disorder	1	1	0.667	1.000	

patients showed significant improvement at 12 weeks. However, in their meta-analysis of 5 RCTs, there was no significant difference between FMT and controls in clinical improvement at 12 weeks (RR1⁄40.93 (95% CI 0.50–1.75) or in quality of life[17]. The results of six RCTs on FMT for IBS are summarized in **Table 3**. Despite the immense variability in study design and delivery of FMT in these studies, there are 3 systematic reviews and meta-analysis in patients with IBS. Xu *et al*. showed no significant difference in global improvement of IBS symptoms at 12 weeks in FMT vs placebo (RR 5 0.93; 95% CI 0.48–1.79). Two RCTs that used FMT through colonoscopy and nasojejunal tube demonstrated a clinically significant improvement in global IBS symptoms. On the contrary, the two RCTs with use of oral capsule for delivery of FMT showed no benefit or even worse outcome in one of them[24]. Another meta-analysis by Ioniro *et al*. also concluded that fresh or frozen donor stool delivered via colonoscopy or nasojejunal tube may be beneficial in IBS. Delivery of FMT by oral capsules was not beneficial[25]. The reasons for these differences may be explained by variation in route of administration and placebo effect. There is evidence to suggest that bowel lavage and colonoscopy by themselvescan alter the fecal microbiota favorably for a few weeks[26]. The response to FMT in our patients with IBS was transient and waned after 8 weeks in the majority of patients. The improvement in symptoms was most apparent at one week after FMT. Some patients felt 'like never before' and even sent thank you notes and texts. It has been shown that there is incremental effect of donor stool on gut flora of the recipient that may be demonstrable as early one week after FMT but it may take three months for the biodiversity to match that of the donor[27]. If FMT was indeed effective for IBS, the improvement should have been most obvious at 12 weeks and even continued beyond. It is quite likely that the transient response in our patients was due to placebo effect. In a meta-analysis of 73 RCTs on treatment of IBS, pooled placebo response was as high as 37.5% (95% CI 34.4-40.6%)[28]. Some experts feel that the delivery of fecal bacteria to the upper GI tract may inadvertently cause an exacerbation of underlying functional GI symptoms.

Table 3: Summary of randomized control trials on FMT for IBS.

Year/author	2018, Johnsen *et al*. 18		2019, Holster *et al*.19		2018, Aroniadis *et al*.20		2018, Halkjaer *et al*. 21		2018, Holvoet *et al*. 22		Magdy El_Salhy23		
Country	USA		Sweden		Norway		Denmark		Belgium		Norway		
Route of administration	Colonoscopy		Colonoscopy		Oral capsules		Oral capsules		Nasojejunal		Endoscopy		
Dose of FMT	30 G		50 to 80 G		0.38G stool/capsule25 capsules/day x 3 days		25 capsules/day x 12 days		NR		30G, 60G		
Placebo	Placebo stool		Autologous		Placebo capsules		Placebo capsules		Autologous		Autologous		
Patient selection	IBS-D, IBS-M		IBS-C, IBS-D, IBS-M Only patients with low Butyrate production		IBS -D		IBS-C, IBS-D, IBS-M		IBS-D, IBS-M		IBS-C, IBS-D, IBS-M		
Number of FMT sessions	1		1		NA		NA		1		1		
Total patients	83		16		48		51		64		163		
Study group	FMT	Control	FMT	Control	FMT followed by control	Placebo followed by FMT	FMT	Placebo	FMT	Control	FMT (30G)	FMT (60G)	Placebo
Sample size	55	28	8	8	24	24	25	26	42	22	54	54	55
Criteria of response	IBS-SSS reduction ≥ 75		30% reduction in GSRS-IBS; Reduction in IBS-SSS		IBSSSreduction≥ 50		Reduction in mean IBS-SSS; IBS-SSS reduction ≥50		Reduction in symptoms (daily diary)		IBSSSreduction≥ 50		
Response at 12 weeks	65%	43%	Not mentioned	Not mentioned	Mean IBS-SSS 221(SD105)	Mean IBS-SSS 236(SD 95)	IBS-SSS -52.45(SD 97.72)	IBS-SSS -125.71(SD 90.85)	49%	29%	77%	89%	24%
	p = 0.049		p = NS		p= 0.65		p = 0.012		p = 0.004		p = <0.001		
Result	Benefit		No benefit		No benefit		No benefit (Placebo better)		Benefit		Benefit		
Microbiota analysis	No		Yes		Yes		Yes		Yes		Yes		
Follow up time	12 months	12 months	6 months	6 months	12 weeks	12 weeks	6 months	6 months	12 weeks	12 weeks	3 months	3 months	3 months
Remarks	QOL Improved		QOL improved No change in visceral sensitivity		No change in QOL, depression, anxiety				QOL improved		QOL improved		
Adverse effects, n (%)	3 (5.45)	3 (10.71)	4 (50)	7 (87.5)	23 (25.3)	24 (100)	22 (88)	15 (57.6)	NR	NR	48 (88.8)	42 (77.7)	12 (21.8)

However, the RCT by El-Salhy *et al*, published after all three meta-analyses, showed that endoscopic delivery of FMT resulted in response at 3 months in 23.6%, 76.9% ($p<0.0001$) and 89.1% ($p<00.0001$) of the patients who received placebo, 30 g FMT and 60 g FMT[23].

It is interesting to note that the criteria of response in the six the RCTs is quite variable. When we analyzed our data based on downgrading of severity of IBS-SSS from severe to moderate/mild or from moderate to mild, reduction in IBS-SSS by 75 or more or a reduction in IBS-SSS by 50 or more, the outcomes remained similar (**Figure 3**). The European Medicines Agency and the US Food and Drug Administration suggest the use of

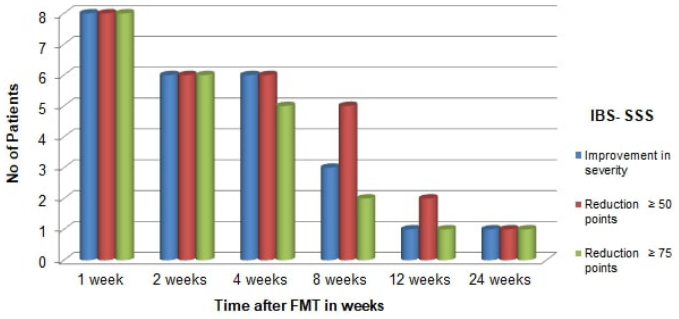

Figure 3:Response to FMT by using different criteria of change in IBS-SSS: improvement in severity, reduction by 50 or more points and reduction by 75 or more points.

reduction in abdominal pain as the primary endpoint and assessing stool frequency as a secondary endpoint in studies on IBS. However, as suggested by the National Task Force on IBS in India, pain abdomen may not be ubiquitous in patients with IBS in our country[29]. Type of IBS did not influence the result of FMT in our study. Majority of patients included in the six RCTs had IBS-D or IBS-M, and very few had IBS-C. It is, however, also well known that patients classified by the same IBS subtype do not necessarily display the same pathophysiology.

Changes in gut microbiota in patients with IBS have been well described. A meta-analysis performed on 13 studies had shown that there were significant differences in expression in IBS patients compared to healthy controls for Lactobacillus, Bifidobacterium, and Faecalibacteriumprausnitzii[30]. The gut microbiota profile of the donor should ideally be able to reinforce the deficient species in patients with IBS. However, as demonstrated by some of the RCTs, favorable changes in gut microbiota may not necessarily correlate with clinical response to FMT[19,20,21,22,23].

Improvement in WHO-QOL, like improvement in IBS-SSS severity, was transient in our patients. One patient had improvement in WHO-QOL despite no improvement IBS-SSS. In a study of 161 patients followed up for 4.7 years, reduction in symptoms of IBS did not correlate with improvement in QOL. Also, higher anxiety and depression scores at follow-up were associated with lower QOL and life satisfaction at follow-up[31]. In a recent double-blind randomized placebo-controlled study on patients with non-constipated IBS, significant improvement in QOL (Odds ratio (OR) 3,801; confidence interval (CI) = 1,309 11,042 p = 0.011) and fatigue (OR = 4,398; CI = 1,175 16,468 and p = 0,020) was found at six months(32).

Adverse events were limited to mild and transient gastrointestinal symptoms in our patients.The adverse effects reported in treatment and placebo arms of all six RCTs are shown in **Table 2**. Response to our questionnaire at one year threw up some information on acceptance of FMT by patients of IBS and willingness to undergo the procedure again. The recipients could discern a change in the odor of their stool following the procedure. The improvement in three of our patients at nine months with return of donor-type stool odor was an observation that may point to a second peak in engraftment of donor microbiota, an aspect that has not been studied. Marked improvement in one of the patients one year following FMT has been reported in one of the RCTs[18].

FMT resulted in significant benefit in symptoms of bloating, frequency of stool and pain abdomen for eight weeks in our study. Symptoms returned to baseline at 12 weeks in the majority. Improvement in depression, and QOL followed the same pattern. Delayed improvement was noted at 9 months after FMT in some patients. Even though our study is limited by open label design, small cohort of patients and absence of data on effect on bacterial flora, we have shown for the first time, that repeated sessions of FMT may not accrue any additional benefit in patients with IBS. Future trials could consider tailoring the use of FMT to various subtypes of IBS by using of donors with a specific gut microbiome profile.

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