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Does Fecal Microbiota Transplantation Improve Disease Severity in Irritable Bowel Syndrome Patients Compared to Placebo?

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not fecal microbiota transplantation improves disease severity in irritable bowel syndrome patients compared to placebo.

STUDY DESIGN: A systematic review of three double-blind, randomized, placebo-controlled trials published since 2014.

DATA SOURCES: Articles found using PubMed, Cochrane Library, AMED and CINAHL Plus and selected based on their relevance to the clinical question. All sources published in peer reviewed journals in English.

OUTCOME(S) MEASURED: Disease severity of irritable bowel syndrome measured in all three studies using the IBS-severity scoring system (IBS-SSS).

RESULTS: The primary endpoint evaluated in all studies was improvement in symptom severity at 3 months after intervention quantified using IBS-SSS. Halkjær et al[3] found a decrease in IBS-SSS of 52.45 ± 97.72 in the FMT group and a decrease in IBS-SSS of 125.71 ± 90.85 in the placebo group (p=0.012). Johnsen et al[1] found 65% of FMT recipients vs. 43% of placebo recipients showed a decrease in IBS-SSS of > 75 points at 3 months after intervention (p=0.049). Aroniadis et al[5] found a decrease in IBS-SSS of 221 ± 105 in the FMT group and a decrease of 236 ± 64 in the placebo group (p=0.65).

CONCLUSIONS: Johnsen et al[1] was the only study to demonstrate a statistically significant difference between the two groups in favor of FMT over placebo. Halkjær et al[3] and Aroniadis et al[5] reported a decrease in symptoms among both FMT and placebo groups with Halkjær et al[3] finding a statistically significant difference in favor of placebo while Aroniadis et al[5] finding no statistical significance between the two groups. These 3 studies show conflicting evidence for the use of FMT in IBS patients although overall it does not appear FMT improves disease severity in IBS patients enough to justify the risk associated with FMT for a non-lethal disease.

KEY WORDS: Fecal microbiota transplant, fecal transplant, and irritable bowel syndrome.

INTRODUCTION

Irritable bowel syndrome (IBS) is a gastrointestinal disorder characterized by abdominal pain associated with changes in frequency or consistency of bowel movements thought to be due in part, to dysbiosis of the gut flora.[1] It can be further categorized into diarrhea-predominant, constipation-predominant, or mixed subtypes and is considered a functional gastrointestinal (GI) disorder that lacks biochemical markers and relies on the Rome III criteria for diagnosis.[2] It is the most commonly diagnosed GI condition affecting 1 in 5 people during their lifetime and greatly affects these patient's quality of life.[3]

It also carries a significant healthcare burden with IBS patients attending between 8.6-9.0 visits with a healthcare provider annually compared to their counterparts without the disease who only attend 4.6 visits per year.[2] These patients also have more emergency room visits and hospitalizations and receive twice as many hysterectomies and three times as many cholecystectomies.[2] In the US, the annual cost per patient with IBS is estimated to be between $742 and $7,547 with a projected total cost of 1.4 billion dollars nationally.[4] Furthermore, it is estimated that the total cost of IBS is comparable to the cost of other highly prevalent chronic illnesses such as hypertension, heart failure, migraines, and asthma,[2] making this an area of interest to save in healthcare costs if a reliable treatment could be established.

Additionally, of those with IBS who seek medical care, 90% of consultations are with a general practitioner,[2] allowing physician assistants to play a large role in managing their care. Usually, IBS treatment begins with reassurance paired with lifestyle and dietary modifications to control symptoms.[2] Pharmacologic treatment is typically limited to antispasmodics for abdominal pain and either laxatives for constipation-predominant symptoms or antidiarrheals for diarrhea-predominant symptoms.[2] IBS has historically been considered a diagnosis of exclusion

and treated symptomatically, however, much is still unknown about the etiology of IBS and better understanding of the pathophysiology of IBS may offer room for new treatments to be explored.

It is currently thought that the microbiota in the GI tract may play a significant role in the etiology of IBS as those with the disease have shown significantly different gut microbiomes than healthy individuals.[3] It has been demonstrated that treatments that target the gut flora such as probiotics, prebiotics, and antibiotics improve IBS disease severity,[5] but whether or not other microbiome altering treatments, such as fecal microbiota transplantation (FMT) could offer relief for these patients has not yet been fully explored. FMT is a procedure where healthy donor stool is infused into a patient with dysbiosis of their gut flora either through endoscope, nasoenteric tube or oral capsules to establish new healthy gut microbiota.[6] When considering other disease states that alter gut microflora, such as C. difficile infections, FMT has been more successful in eradicating the infection than standard therapies.[3] Its success is thought be due to restoring healthy gut microbiota, suggesting this method may offer possible benefit to those with IBS as well.[3] This paper evaluates three double blind randomized controlled trials comparing the efficacy of FMT on IBS disease severity compared to placebo.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not fecal microbiota transplantation improves disease severity in irritable bowel syndrome patients compared to placebo.

METHODS:

Three double-blind, randomized, placebo-controlled trials were chosen for review. Articles were selected for review based on searches using the key words “fecal microbiota

transplant", "fecal transplant", and "irritable bowel syndrome" using PubMed, Cochrane Library, AMED and CINAHL Plus. Articles were selected based on their relevance to the clinical question, if they addressed patient oriented outcomes (POEMs), and if they met the inclusion and exclusion criteria. Inclusion criteria included randomized controlled trials (RCT) published since January 2014 and exclusion criteria included all studies published prior to January 2014 and those that were not RCTs. Each article was published in a peer reviewed journal in the English language. The statistics reported and used in this systematic review were p-values and mean change from baseline. Table 1 below provides more detail on the demographics and characteristics of the three studies chosen for review.

The population being studied in this review is adults 18-75 years old diagnosed with IBS according to Rome III criteria with an IBS-severity scoring system (IBS-SSS) $\geq$ 175. The intervention in each study was FMT and comparison used was placebo. Authors Halkjær et al[3] and Aroniadis et al[5] delivered FMT via oral capsules and used placebo capsules as comparison. Author Johnsen et al[1] delivered FMT via colonoscope and used patients own feces as comparison. Outcomes obtained in all 3 studies were IBS disease severity as measured by IBS-SSS.

OUTCOMES MEASURED:

Outcomes were measured via the IBS-severity scoring system (IBS-SSS). This is a self-assessment questionnaire that evaluates the intensity of patient's abdominal pain, distention, stool frequency and consistency, and interference in daily activities.[1] Each of those five items is scored on a visual analog scale from 0-100 and then summed for a total score of 0-500.[3] Scores between 175-300 indicate moderate disease severity and scores over 300 indicate severe

disease.[1] Study participants in each RCT completed the questionnaire before, during and after receiving the intervention.

Table 1 - Demographics & characteristics of included studies

Study	Type	# of Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	w/d	Interventions
Halkjær[3] (2018)	RCT	52	36.4 ± 11.5	Pts diagnosed with IBS via Rome III criteria between 18-60 yrs old with an IBS-SSS ≥ 175, normal colonoscopy in the last year if the pt was ≥ 40 or had blood in their stool.	Pts with other GI illnesses, fecal sample positive for enteropathogenic microorganisms or calprotectin ≥50, Recent use of probiotics/antibiotics, psychiatric disorders, HIV, HBV or HCV positive, select surgical interventions and medications, alcohol/drug abuse, pregnant or breastfeeding	7	25 FMT capsules totaling approx. 12g of feces taken by mouth once daily for 12 days with water 1 hour before eating vs. placebo capsules.
Johnsen[1] (2018)	RCT	87	33-57	Pts diagnosed with IBS via Rome III criteria, between18-75 yrs old with an IBS-SSS ≥ 175. Pts with IBS-diarrhea predominant or mixed type.	Pts with IBS-constipation predominant, severe cardiac or pulmonary disease, kidney failure or immune compromise, recent antibiotic use or those with suspected alternative diagnoses to IBS.	4	50-80g of fresh or frozen feces delivered by colonoscope to the cecum vs patient's own feces as placebo.
Aroniadis[5] (2019)	RCT	48	27-48	Pts diagnosed with IBS-diarrhea predominant via Rome III criteria, between 18-65 yrs old with an IBS-SSS ≥ 175.	Pts with constipation predominant or mixed subtype, pregnant, immune compromise, any diagnosis of a GI illness alternative to IBS or recent antibiotic or probiotic use.	3	25 FMT capsules (.38g of feces each) taken orally with water on 3 consecutive days vs. placebo capsules.

RESULTS:

Halkjær et al[3] conducted a six month randomized, double-blind, placebo-controlled study of 52 adults with moderate to severe IBS based on inclusion/exclusion criteria presented in Table 1 above. The participants were randomized into two demographically comparable groups of 26.[3] At 3 months, the FMT group had 1 patient lost to follow up and 1 excluded from analysis due to antibiotic treatment and the placebo group had 1 excluded from analysis due to probiotic treatment.[3] The group receiving the intervention was instructed to orally ingest 25 capsules of mixed donor FMT each morning before eating for 12 consecutive days.[3] Each daily dosage of FMT contained approximately 12g of fecal matter for a total of 144g of FMT ingested.[3] The control group also followed this protocol but consumed capsules made of glycerol, saline and food coloring E150.[3]

Participants were surveyed using the IBS-SSS and fecal samples collected at baseline, 1, 3 and 6 months.[3] The primary endpoint evaluated was mean change from baseline at 3 months in the two groups as to keep interpretation of outcomes the same among the three studies. Those receiving FMT had a decrease in their IBS-SSS of 52.45 ± 97.72 and those receiving placebo had a decrease of 125.71 ± 90.85 resulting in a statistically significant improvement in symptom severity among the placebo group ($p=0.012$) as seen in Table 2.[3]

Twenty-two patients in the FMT group (84.6%) and 15 in the placebo group (57.7%) experienced adverse effects during the study although no side effects were more predominant in the FMT group compared to placebo except diarrhea ($p=0.03$).[3] A complete list of adverse effects can be found in Table 3 below.

Table 2 – Mean (SD) change in IBS-SSS from baseline to 3 months and statistical significance data from Halkjær et al[3]

	At baseline (mean (SD))	Third month (mean(SD))	Mean change from baseline (mean (SD))	P- value
FMT group	341.68 (95.02)	287.14 (118.30)	52.45 (97.72)	0.012
Placebo group	345.04 (79.56)	218.96 (121.87)	125.71 (90.85)	

Table 3 – Adverse effects from Halkjær et al[3]

	Abd pain	Nau-sea	Dia-rrhea	Head-ache	Bloat-ing	Em-esis	Fat-igue	Gas	Dizzy	Fev-er	Obsti-pation	Re-flux
FMT group	7 27%	9 35%	6 6%	3 12%	5 19%	1 4%	1 4%	3 12%	2 8%	2 7%	3 12%	2 8%
Placebo group	5 19%	7 27%	0 17%	3 12%	1 4%	0	4 15%	1 4%	0	0	0	3 12%
p-value	0.74	0.76	0.03	1.0	0.19	1.0	0.35	0.60	0.47	0.47	0.23	1.0

Johnsen et al[1] conducted a double-blind, randomized, placebo controlled study of 90 participants and randomized them into 3 groups of 30 based on inclusion/exclusion criteria presented in Table 1. One group received fresh FMT, one received frozen FMT and one received placebo.[1] Two participants were lost to follow up in both the fresh FMT and placebo groups.[1] In this study, 50-80g of either fresh or frozen donor feces or the patient's own feces serving as placebo was mixed with saline and glycerol delivered via colonoscope to the cecum.[1] Loperamide 8mg was administered to both groups 2 hours prior in order to retain the transplant.[1] The primary endpoint evaluated was symptom relief of more than 75 points as assessed via IBS-SSS from baseline to 3 months after intervention.[1] Participants completed the IBS-SSS at baseline, 1, 3, 6, and 12 months after intervention.[1] Analysis revealed 65% of FMT recipients vs. 43% of placebo recipients showed a decrease in IBS-SSS of > 75 points at 3 months after intervention (p=.049).[1]

Further analysis revealed those who received frozen FMT had a larger change in IBS-SSS from baseline than fresh FMT as demonstrated in Table 4 below.[1] One serious adverse event occurred with a patient requiring hospital admission for observation after experiencing nausea and vertigo post transplant.[1] Otherwise, mild adverse events are reported in Table 5 below.

Table 4 – Mean change in IBS-SSS from baseline to 3 months and statistical significance data from Johnsen et al[1]

	At baseline (mean)	Third month (mean)	Mean change from baseline (calculated)	P- value
Fresh FMT	260	150	110	.049
Frozen FMT	280	155	125	
Placebo	278	250	28	

Table 5 – Adverse events from Johnsen et al[1]

	FMT	Placebo
Soiling of transplant	1 (.02%)	1 (.03)
Abdominal pain	1 (.02%)	2 (.07%)
Nausea and vertigo	1 (.02%)	0

Aroniadis et al[5] conducted a 6 month double blind, randomized, placebo controlled trial that featured a crossover design. Twenty-five patients were assigned to receive FMT first and 23 were assigned to receive placebo first.[5] Three participants in the FMT first group were lost to follow up before 3 months and were excluded from analysis while none were lost to follow up in the placebo first group.[5] All patients crossed over to the alternate intervention at 3 months.[5] In order to maintain consistency with the other studies being evaluated only the first arm of the crossover trial will be evaluated.

The FMT first group ingested 25 oral capsules each containing 0.38g of single donor stool on 3 consecutive days for a total of 75 capsules and 28.5g of feces.[5] The placebo group ingested placebo capsules of nontoxic brown pigment to mimic the FMT capsules.[5] Both were

administered with PPI to prevent lysis in the upper GI tract.[5] Participants were surveyed at baseline, 1, 4, 12, 13 , 16 and 24 weeks after dosing via IBS-SSS and fecal samples were collected at each time.[5] At baseline, the FMT first group's IBS-SSS scores were 282 ± 65 and the placebo first group's scores were 309 ± 64, (p=0.15).[5] At 3 months the FMT first group's scores were 221± 105 and the placebo first group's scores were 236 ± 64 (p=0.65)[5] indicating the results were not statistically significant and therefore it cannot be concluded that any significant difference exists between the two groups. A calculated mean change from baseline for each groups revealed a 61 point decrease in symptom severity in the FMT first group and a 73 point decrease in the placebo first group as shown in Table 6 below. Additionally, participants receiving placebo had a higher clinical response rate (61%) at 12 weeks than the FMT group (50%) although not statistically different (p=0.46).[5] Overall, 47 adverse events related to the study drugs occurred during the 6 months with 23 related to FMT and 23 related to placebo although no difference was found between the groups as shown in Table 7 below.[5]

Table 6 – Mean (SD) change in IBS-SSS from baseline to 3 months and statistical significance data from Aroniadis et al[5]

	At baseline (mean (SD))	Third month (mean (SD))	Mean change from baseline (calculated)	P- value
FMT group	282 (65)	221 (105)	61	0.65
Placebo group	309 (64)	236 (95)	73	

Table 7 – Adverse events reported from Aroniadis et al[5]

	Abd pain	Nausea	Diarrhea	Consti-pation	Bloating	Emesis	Fatigue	Gas	Belch-ing	Anorex-ia
FMT group	5 10%	4 8%	3 6%	2 4%	2 4%	2 4%	2 4%	1 2%	1 2%	1 2%
Placebo group	4 8%	2 4%	8 17%	0	5 10%	0	1 2%	4 8%	0	0
p-value	>.99	0.68	0.20	0.24	0.44	0.50	>.99	0.36	>.99	>.99

DISCUSSION:

Some degree of improvement in disease severity was noted in all FMT groups across the three studies although this was not always statistically significant and symptom improvement was seen among groups receiving placebo as well. While Johnsen et al[1] found a statistically significant treatment effect in favor of FMT ($p=0.049$) this effect was small and Halkjær et al[3] found a statistically significant treatment effect ($p=0.012$) in favor of placebo. Furthermore, Johnsen et al[1] demonstrated 65% of FMT recipients showed a decrease in IBS-SSS of > 75 points at 3 months which equates to greater than a 15% reduction in symptoms. However, this translates to the remaining 35% of participants experiencing a decrease in symptoms by less than 15%. Additionally, in Aroniadis et al[5], both placebo and FMT groups had similar reductions in disease severity, with neither reaching more than a 15% reduction in symptoms. These modest improvements in symptoms after FMT likely do not warrant recommending FMT over conservative therapies to IBS patients at this time.

While the three studies demonstrated that FMT was not inherently harmful, numerous mild adverse effects were noted in all studies and the risks associated with FMT may limit its practical application. With colonoscope delivery there is a risk of bowel perforation and intolerance to anesthesia.[7] Since IBS is a non-lethal disease the risks associated with an intervention should be minimized as much as possible.

Limitations in all three studies are small sample size, making generalizations to larger populations challenging and statistical significance difficult to prove. Halkjær et al[3] and Aroniadis et al[5] recruited participants from European countries while Johnsen et al[1] recruited patients from the United States creating an opportunity for confounding variables such as diet and environment to effect study outcomes as lifestyle factors are known to play a role in IBS.

Lastly, a limitation of this review is that IBS-subtype studied and amount and type of fecal matter transplanted was not consistent across all three studies making it difficult to conclude which IBS subtype(s) would most be effected by FMT, at what appropriate dose, and if single or mixed donor stool should be utilized.

CONCLUSION:

Findings are inconclusive if FMT is better at reducing IBS disease severity compared to placebo. Halkjær et al[3] and Aroniadis et al[5] did not find that FMT improved disease severity compared to placebo while Johnsen et al[1] did find statistically significant symptom improvement among those who received FMT compared to placebo. However, it is important to note that placebo improved symptom severity in all studies as well. Due to both placebo and FMT demonstrating minor symptom improvement in all 3 studies, it is reasonable to conclude that FMT does not improve symptom severity in IBS patients compared to placebo. Symptom improvement of this magnitude could likely be achieved with more conservative measures and the data does not support utilizing FMT over current treatment regimens for a modest improvement in symptoms.

Since many individuals with IBS purchase over the counter medications to remedy their symptoms it is difficult to quantify the cost burden per patient.[4] Studies on the cost effectiveness of FMT for IBS treatment have not yet been performed however, studies have shown than using FMT via colonoscope for recurrent C. difficile infections is in fact more cost effective than traditional antibiotic regimens.[7] Thus, additional longitudinal studies in this area to evaluate cost effectiveness and continuity of symptom improvement would benefit clinical decision making when it comes to using FMT as a treatment for IBS. Additionally, FMT delivered orally via capsules tend to be faster, cheaper, and better tolerated.[7] Further research into FMT delivered

orally may offer safer treatment options if proven to be an effective intervention with additional RCTs. Additionally, larger studies with more diverse patient populations will be required before any change to current clinical practice should be proposed. All three RCTs recruited sample sizes under 90 participants and the participants in the study by Aroniadis et al[5] were predominately male (64%) when IBS is more commonly diagnosed in females. However, according to the Cochrane Library's CENTRAL trials database, 41 ongoing trials evaluating FMT and IBS have been added to the database in the last 2 years, with 9 published in 2020 alone. This confirms this is an area of increased interest in the medical community and indicates our knowledge on the topic will continue to grow and offer a better understanding of this novel approach to IBS treatment.

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