12-2017

Does Fecal Microbiota Transplantation Cause Clinical Remission in Patients with Ulcerative Colitis?

Amandeep Singh
Philadelphia College of Osteopathic Medicine

"Does Fecal Microbiota Transplantation cause Clinical Remission in Patients with Ulcerative Colitis?"

Amandeep Singh, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 16, 2017

Abstract

Objective: The objective of this selective EBM review is to determine whether or not "Does Fecal Microbiota Transplantation cause Clinical Remission in Patients with Ulcerative Colitis?"

Study Design: Review of three English language primary studies published in 2015.

Data Sources: Two randomized control trials and a cohort study determining if fecal microbiota transplantation does lead to clinical remission of Ulcerative Colitis were found by using PubMed and Cochrane databases.

Outcome(s) Measured: The outcomes measured in all three studies were patient oriented evidence that matters which is clinical remission. The outcomes in the Moayyedi et al. was measured by the Mayo Score The Rossen et al. study determined clinical remission as SCCAI score ≤ 2 in combination with ≥ 1 point improvement on the combined Mayo endoscopic score of the sigmoid and rectum, compared to the baseline sigmoidoscopy, 12 weeks after the first treatment. The Wei et al. trail determined clinical remission was defined as IBDQ >170 and Mayo score <2 in Ulcerative Colitis.

Results: This review compares two randomized, double blind, placebo controlled clinical trials and one cohort study in which the Moayyedi et al. and Wei et al. trial proved that Fecal microbiota transplantation is effective in providing clinical remission in patients with active Ulcerative Colitis; however, the Rossen et al. trial showed there was no significant statistical difference between the experimental [FMT-D] and the placebo [FMT-A] group in inducing clinical remission in patients with active Ulcerative Colitis.

Conclusions: Fecal Microbiota Transplantation does seem to provide effective treatment in causing clinical remission of Ulcerative Colitis overall according to the three studies in this review.

Key Words: fecal microbiota, Ulcerative Colitis

INTRODUCTION

Ulcerative Colitis results from an abnormal response by the body's immune system. The immune system normally contains proteins and cells that protect the body from infection; however, in Ulcerative Colitis, the immune system mistakes food, bacteria, and other material in the intestine as foreign or infectious substances.[1] This immune system impairment leads to a chronic disease of the colon in which the mucosal lining of the colon becomes inflamed, leading to diffuse friability and erosions which result with open sores or ulcers producing pus, mucus, and bleeding.[2] Patients with ulcerative colitis usually present with bloody diarrhea. Bowel movements are frequent and small in volume as a result of rectal inflammation. Some other associated symptoms include colicky abdominal pain, urgency, tenesmus, and incontinence. Patients with mainly distal disease may have constipation accompanied by frequent discharge of blood and mucus.[3] Although considerable progress has been made in IBD research, investigators do not yet know what causes this disease.

Ulcerative colitis affects 907,000 people in the United States, and is currently on the rise with 38,000 new cases each year.[4] Men and Women are equally likely to be affected, with most diagnosed in their mid-30s.[4] However, Ulcerative Colitis can occur at any age and recent studies showed older men are more likely to be diagnosed than older women.[4] The annual direct cost based on US insurance claims data from 2003-2004 is $5,066 per patient, indirect costs were $5,228 per patient, and the annual financial burden of IBD in the US may be more than $31 billion.[4]

Currently there is no definitive cure for Ulcerative Colitis but there are medications currently out to provide symptomatic relief to treat the disease. The initial therapy for a patient with Ulcerative Colitis is patient education; eat regular diet but limit intake of caffeine and gas-

producing vegetables. Anti-diarrheal agents should not be given in the acute phase of the illness but are safe and helpful in patients with mild chronic symptoms. For symptomatic relief, medications are taken such as oral 5-ASA agents such as mesalamine, balsalazide, or sulfasalazine. If no improvement is seen on 5-ASA after 4-8 weeks of improvement then add on corticosteroids such as prednisone or methylprednisolone. Patients not responding to 5-ASA or corticosteroids or for corticosteroid-dependent patients give immunomodulators such as Mercaptopurine or azathiopurine or an Anti- TNF like Infliximab. If all these medications don't work then last resort is surgery to remove the diseased portion of the colon.[2]

In Ulcerative Colitis the composition of the microbiota is different in that of a healthy individual in that the diversity is lower and contains lower number of Clostridium clusters and Bacteriodes. It is unclear if this disturbed microbiota is the cause or result of UC.[5] Fecal microbiota transplantation may offer a method of enriching the gut microbiota leading to remission of Ulcerative Colitis.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not fecal microbiota transplantation cause clinical remission in patients with Ulcerative Colitis.

METHODS

These three studies, two randomized controlled trials and one cohort study, this systematic review was based on the population age, the intervention, and the outcomes measured. The populations of the research article were all adults, both males and females, ages 18-70 year old, diagnosed with active or established Ulcerative Colitis. The common

intervention among all studies was transplantation of fecal microbiota. The demographics and characteristics of each study are displayed in Table 1. For the study by Moayeddi et al, the comparison groups were patients with Ulcerative Colitis given Fecal Microbiota Transplantation (FMT) from healthy donor versus Patient given a placebo.[6] Patients were randomized in this study to either receive 50 mL of FMT or a placebo of 50 mL of water given as a retention enema once per week for a total of 6 weeks. On the seventh week, patients returned to complete the final Mayo Clinic Score, Inflammatory Bowel Disease Questionnaire (IBDQ) and an exit sigmoidoscopy to compare to the baseline scores.[6] In the Wei et al study, there was no comparison study and just measured the results of patients receiving FMT over a 4 week period. The way this transplantation procedure took place was the participants were maintained on 500 mg of vancomycin twice a day, for three consecutive days 12 hours before the Fecal Microbiota Transplantation (FMT). On the day before the procedure participants also took polyethylene glycol to wash out any fecal material and then the 300 mL donor material was administered by a colonoscopy's biopsy channel.[7] In the Rossen et al study, the comparison groups were patients with Ulcerative Colitis, were randomized either receiving 2 duodenal infusions of donor feces from healthy host [FMT-D] or 2 duodenal infusions of autologous feces [FMT-A] which served as a control in participants receiving their own feces. This was administered via nasoduodenal tube. Prior to the administration, patients were pretreated with bowel lavage the evening and morning before the treatment to washout much of the particpants indigenous microbiota.[5] Three weeks later the same procedure was repeated and the outcomes were measured at week 12. The outcome in these 3 studies, which were important, was Clinical Remission that qualifies as patient oriented evidence that matters (POEM).

Keywords used in the searches were “fecal microbiota and Ulcerative Colitis.” All articles were published in peer-reviewed journals in the English language. The articles were searched through the Cochrane databases and through PubMed. The articles were patient oriented evidence that matters (POEM). Inclusion criteria for this study is randomized control trials and cohort studies based on patient oriented evidence that matters, patients aged 18 or older with active Ulcerative Colitis defined as Mayo Clinic The exclusion criteria for this study are patients under the age of 18, articles that were not randomized double blind, articles without placebo controlled trails, and disease oriented trials. The statistics reported in this study were p-values, Relative Benefit Increase (RBI), Absolute Benefit Increase(ABI), number needed to treat (NNT).

Table 1: Demographics & Characteristics of included studies

Study	Type	#pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	w/d	Intervention
Moayyedi P (2015)	Randomized Controlled Study (RCT)	75	18-60	-Eligible Patients were 18 years or older with active Ulcerative Colitis defined as Mayo Clinic Score 4 with an endoscopic Mayo Clinic Score 1. - Concomitant treatment for UC, such as mesalamine, glucocorticoids, immunosuppressive therapy, or tumor necrosis factor antagonists were permitted, provided these had been used for at least 12 weeks(4 weeks for glucocorticoids) and disease remained active. - 5 patients who were previously exposed to mesalamine or steroids had a 30 day washout period before being enrolled.	Pt taken antibiotics or probiotics in last 30 days, had concomitant C difficile infection or another enteric pathogen, had a disease severity that required hospitalization, were pregnant, or were unable to give informed consent.	5	Fecal Microbiota Transplantation by Healthy Donor (Retention Enema Approach)
Wei Y (2015)	Cohort Study	11	24-70	-Age Range 18-70y/o -CDAI Score of 150 and 400; or Mayo score(UCDAI) of 2-10.	-Pregnant - End-Stage Disease - If pts participating in other trials within 3 months prior to transplantation. If infectious colitis - Pt scheduled for abdominal surgery - If pt took probiotics/prebiotics/synbiotics/antibiotic/PPI orally in the last month - If pt suffer from severe anemia, heart cerebrovascular accident, and bypass or underwent stent implantation last 6 months - If pt has coagulation disorders or immune suppression status or underwent abdominal transplant last 3 months. - If pt took TNF monoclonal antibody 2 months before transplantation or planned to take it within one month after transplantation. - If pt had history of megacolon.	1	Fecal transplantation from healthy donors (via colonoscopy biopsy channel in UC cases)
Rossen (2015)	Randomized Controlled Study (RCT)	50	30-56	- Established Ulcerative Colitis according to the Leonard Jones Criteria, a pt reported SCCAI of ≥4 and ≤11 and stable medication, which was continued during the study period. - Subjects allowed stable doses of thiopurines, mesalamine, or corticosteroids ≤ 10mg/d for 8 weeks before inclusion. - An endoscopic score ≥1 at baseline sigmoidoscopy was mandatory for inclusion.	- Pt excluded if used anti-tumor necrosis factor or methtroxate treatment within 8 weeks before inclusion, or cyclosporine within 4 weeks before inclusion. - An infectious cause of a Ulcerative Colitis disease flare - Hx of colonectomy, a current stoma, life expectancy <12 months, pregnancy, and hospital admission were exlusion criteria. - Pts were not allowed to use antibiotics or probiotics within 6 weeks before inclusion.	2	- Fecal Microbiota Transplantation from Healthy Donors. - 2 Duodenal Infusions of a suspension of Donor Feces [FMT-D] vs. 2 Duodenal Infusions of a suspension of Autologous Feces [FMT-A]

Outcomes Measured

The outcomes measured in all three studies were patient oriented evidence that matters which is clinical remission. The outcomes in the Moayyedi et al. was measured by the Mayo Score which is a composite of subscores from four categories, including stool frequency, rectal bleeding, findings of flexible proctosigmoidoscopy or colonoscopy, and physician's global assessment, with a total score ranging from 0–12. Within the endoscopic component of the Mayo Score, a score of 0 is given for normal mucosa or inactive UC, while a score of 1 is given for mild disease with evidence of mild friability, reduced vascular pattern, and mucosal erythema. A score of 2 is indicative of moderate disease with friability, erosions, complete loss of vascular pattern, and significant erythema, and a score of 3 indicates ulceration and spontaneous bleeding. Mucosal healing has been defined as a Mayo endoscopic sub score of 0 or 1 in major trials of biological therapies in UC.[6] The Moayyedi et al. study determined clinical remission which is defined as full Mayo Score <3 and an endoscopic Mayo Clinic Score=0.[6] The Rossen et al. study determined clinical remission as SCCAI score ≤ 2 in combination with ≥ 1 point improvement on the combined Mayo endoscopic score of the sigmoid and rectum, compared to the baseline sigmoidoscopy, 12 weeks after the first treatment.[5] The Wei et al. trail determined clinical remission was defined as IBDQ >170 and Mayo score <2 in Ulcerative Colitis.[7]

Results

The Moayyedi et al study was a randomized double blind control study with outcomes that were dichotomous data and based on intent to treat. To begin this study there were 85 patients who were assessed and eligible for the trial. Ten patients from the study were soon dropped due to 7 subjects no longer having active disease, 2 for being clostridum dificile-positive and 1 withdrew before randomization. So 75 patients were left to be randomized into the

placebo group and other half allocated to the FMT trail. 37 patients were in the placebo group and 38 patients were in the FMT experimental group. Patients were randomized in this study to either receive 50 mL of FMT or a placebo of 50 mL of water given as a retention enema once per week for a total of 6 weeks and on the 7th week final Mayo Clinic score, Inflammatory Bowel disease questionnaire (IBDQ) and an exit sigmoidoscopy to compare to the baseline scores. 3 people dropped out from the placebo group and 2 from the FMT experimental group leading to 70 patients completing the study; 34 completing the placebo trial and 36 completing FMT experimental trail. The outcomes were measured for clinical remission at the seventh week after treatment. At the of 7 weeks, the clinical remission of Ulcerative Colitis showed a significant difference in adequate relief between the placebo group and fecal microbiota transplantation experimental group. The proportion of participants in the FMT group that had clinical remission was 23.7% whereas 5.4% of the placebo group had clinical remission (Table 2). With p-value of .03 is statistically significant there is clinical remission of Ulcerative Colitis given FMT compared to placebo.[6]

Table 2: Percent of Participants with Clinical Remission of Ulcerative Colitis 6 weeks after Treatment

	# of Participants in Group	# of participants with Clinical Remission	% of participants with Clinical Remission
Fecal Microbiota Transplantation [FMT]	38	9	23.7%
Placebo	37	2	5.4%

This data from above in Table 2 shows the control event rate [CER] is 5.4%. On the other hand, the experiment event rate [EER], which included the FMT GROUP, is 23.7%. From this data the numbers needed to treat was 6, so for every 6 patients administered Fecal Microbiota Transplantation, one more patient will have remission of Ulcerative Colitis compared to the placebo at 7 weeks.

The Rossen et al. study was a randomized double blind control study with dichotomous data and based on intention to treat. In the Rossen et al. study, 50 patients were randomized into the experimental and control groups and received 2-duoudenal infusions of donor feces from healthy host [FMT-D] or 2-duodenal infusions autologous feces [FMT-A], which is the placebo. Only 48 patients completed the study; 23 in the FMT-D and 25 in the FMT-A group. The infusions were administered at week 0 and week 3 and the outcomes were recorded at the end of 12 weeks from the SCCAI score and combined Mayo endoscopic score. The proportion of participants from the experimental group [FMT-D] group that had clinical remission was 30.4% whereas the proportion of the placebo group [FMT-A] that had clinical remission was 20%. So based on the p-value of .51 data did not show a statistical significant difference in the clinical remission between the placebo and experimental group.[5]

Table 3: Percent of Participants with Clinical Remission of Ulcerative Colitis 12 weeks after treatment

	# of Participants in Group	# of participants with Clinical Remission	% of participants with Clinical Remission
FMT-D	23	7	30.4%
FMT-A	25	5	20%

The data from above shows that the control event rate [CER], which involved the FMT-A group is 20%. On the other hand, the experimental event rate [EER], which is the FMT-D group is 30.4%. The numbers needed to treat is 10, so for every 10 patients administered fecal microbiota transplantation from healthy donor one more patient will have remission of Ulcerative Colitis compared to FMT-A group at the end of 12 weeks.

In the Wei et al. study, which was a cohort study with outcomes was presented as continuous data but was able to be converted into dichotomous data. In this study there were 11 patients with Ulcerative Colitis that were treated with FMT via colonoscopy or nasojejuanal tube infusion. At the end of 4 weeks Inflammatory Bowel Disease Questionnaire, which measured

quality of life, and Mayo score was calculated and compared to the baseline. There was no control study.[7]

Table 4: Results based on Mean Change 4 weeks after Fecal Microbiota Transplantation

	Baseline Score	4 week after treatment Score
IBDQ Score	135.50	177.30
Mayo Score	5.80	1.50

Based on the table above the mean Mayo score in Ulcerative Colitis patients decreased significantly from baseline score of 5.80 to 1.50 which shows dramatic decrease in Mayo Score <2. With a p-value <.01, it provides statistical significance that there is clinical remission of Ulcerative Colitis 4 weeks post treatment. Also, the IBDQ score rose significantly in patients from baseline starting from 135.50 to 177.30 with end IBDQ score >170. With a p-value of 0.00063, it provides statistical evidence that there is Clinical Remission of Ulcerative Colitis 4 weeks post treatment.

Discussion

Ulcerative Colitis is a chronic disease of the colon in which the mucosal lining of the colon becomes inflamed which can lead to open sores or ulcers producing pus, mucus, and bleeding.[2] Currently there is no definitive cure for Ulcerative Colitis but there are medications currently out to provide symptomatic relief to treat the disease. In Ulcerative Colitis the composition of the microbiota is different in that of a healthy individual in that the diversity is lower and contains lower number of Clostridium clusters and Bacteriodes.[5] So it is ambiguous if this disturbed microbiota is the cause of UC. Fecal microbiota transplantation enriching the gut microbiota leading to remission of Ulcerative Colitis.[5]

This review compares two randomized, double blind, placebo controlled clinical trials and one cohort study in which the Moayyedi et al. and Wei et al. trial proved that Fecal

microbiota transplantation is effective in providing clinical remission in patients with active Ulcerative Colitis; however, the Rossen et al. trial showed there was no significant statistical difference between the experimental [FMT-D] and the placebo [FMT-A] group in inducing clinical remission in patients with active Ulcerative Colitis.

These three articles did contain some limitations in this review. In the Moayeedi et al. study, the donor stool was not held as a control as patients either received as frozen or fresh fecal sample. Seemed as if frozen stool seemed to be a bit more effective but may be confounded due to frozen stool being from Donor B. Patients who received Donor B stool seemed to be most effective so not all donor stools effective in treating UC because each stool made of differing microbiota. So another way to keep a better control was all patients received fecal sample from same host to prevent any variables. Another limitation was not performing colonoscopy at study exit and it is possible that patients with extensive colitis have active disease beyond the limit of the flexible sigmoidoscope. Another limitation was a small sample size.[6] Some limitations in the Rossen et al. study is small sample size. Another limitation is inconsistent dosages of fecal transplants every 3 weeks. Another limitation in this particular study is making sure all fecal matter is composed of similar microbiota to make sure treatment is specific-to-specific microbiota, which might yield data on selecting beneficial groups for donation instead of whole microbiome transplantation.[5] The limitations in the Wei et al. trials are small sample size as well as not having a control.[7]

Conclusion

Fecal Microbiota Transplantation does seem to provide effective treatment in causing clinical remission of Ulcerative Colitis overall according to the three studies in this review. Further study is needed to really evaluate the long term effects with the treatment of Fecal

microbiota transplation and to see if it is sustainable in providing long term favorable results. Further studies should include larger sample size, controlled donor feces with similar microbiota, controlled route of administration either colonoscopy or retention enema approach, and should focus on the effect of FMT on clinical remission for periods longer than 4-7 weeks and follow up with patient long term for at least 5 years.

References

1. CCFA: Facts about inflammatory bowel disease. Crohn's & Colitis foundation of america web site. . (http://www.ccfa.org/what-are-crohns-and-colitis/what-is-ulcerative-colitis/. Published 2016. Updated 2016. Accessed 12/01, 2016.

2. Papadakis MA, McPhee SJ, Rabow MW. Current Medical Diagnosis and Treatment: 2016. United States: McGraw-Hill Professional; October 1, 2015.

3. Peppercorn MA, Kane SV. Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adult. Uptodate.com Web site. https://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-prognosis-of-ulcerative-colitis-in-adults?source=search_result&search=ulcerative%20colitis&selectedTitle=1~150#PATIENT_INFORMATION. Published 11/2016. Updated 2016. Accessed 12/01, 2016.

4. CCFA: Facts about inflammatory bowel disease. Crohn's & Colitis Foundation of America Web site. http://www.ccfa.org/assets/pdfs/updatedibdfactbook.pdf. Published November 2014. Updated 2014. Accessed 10/09, 2016.

5. Rossen NG, Fuentes S, van der Spek MJ, et al. Findings from a randomized controlled trial of fecal transplantation for patients with ulcerative colitis. *Gastroenterology*. 2015;149(1):110-118.e4. doi: 10.1053/j.gastro.2015.03.045 [doi].

6. Moayyedi P, Surette MG, Kim PT, et al. Fecal microbiota transplantation induces remission in patients with active ulcerative colitis in a randomized controlled trial. *Gastroenterology*. 2015;149(1):102-109.e6. doi: 10.1053/j.gastro.2015.04.001 [doi].

7. Wei Y, Zhu W, Gong J, et al. Fecal microbiota transplantation improves the quality of life in patients with inflammatory bowel disease. *Gastroenterol Res Pract*. 2015;2015:517597. doi: 10.1155/2015/517597 [doi].