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Research Article

Treating Refractory Clostridium Difficileby Fecal MicrobiotaTransplant Does Not Alter the Course of Underlying Inflammatory Bowel Disease in Children

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Abstract:

Fecal Microbiota Transplant (FMT) has been proven to be very effective for eradicating Clostridium Difficile Infection (CDI) refractory to antibiotics. Some reports suggest that FMT may also be useful in altering the course of Inflammatory Bowel Disease (IBD). Our objective is to assess IBD patients who received a single FMT for CDI and see if it altered the clinical course of their IBD. In review of Mayo clinic records between 2013 and 2015, nine patients meeting criteria were identified (7 males, 2 females with average age of 13.8). We used Physician Global Assessment and traced IBD medication changes in order to determine patients' status before and after FMTs. All patients showed clinical improvement post-FMT, this improvement was attributed to CDI eradication. None of our nine patients stopped their IBD maintenance therapy following FMT. Eight patients (88%) had IBD relapses at some point following FMT and had a step up in their therapy. The results from our series show that benefits of FMT on IBD may be limited. FMT does not alter the course of the underlying IBD beyond the acute treatment of CDI.

Keywords: Clostridium Difficile Infection (CDI); Fecal Microbiota Transplant (FMT); Inflammatory Bowel Disease in Children

Introduction:

Clostridium Difficile Infection (CDI) is a relatively common condition in both children and adults with almost half a million (453,000) infections per year in the United States alone [1]. This anaerobic bacillus is found to flourish and colonize the colon especially in cases where the gut's normal flora has been altered. Antibiotics remain the primary therapy for CDI as they successfully eradicate up to 80% of cases. For the remaining 20% who relapse once antibiotics are stopped a fecal microbiota transplant (FMT) is indicated [2,3]. FMT is very effective at eradicating relapsing CDI; a review of more than 500 reported cases showed a mean cure rate of 87% to 90% [4].

CDI in patients with underlying Inflammatory Bowel Disease (IBD) is not uncommon given the frequent use of antibiotics and immunosuppressants in this population [5]. CDI tends to have a negative impact on IBD course, where patients require hospitalization and escalation in IBD therapy more frequently than controls [6]. FMT is found to be effective and safe when treating relapsing CDI in IBD patients [7, 8]. However, reports described an additional effect on the underlying IBD as improved response to IBD medication. In addition, there are case reports and one series suggesting that FMT can be used as an induction or maintenance therapy for IBD, with patients showing resolution of symptoms or even cessation of maintenance therapy [9,10]. We therefore assessed our group of pediatric IBD patients who received a single FMT for recurrent CDI to see if it went beyond treating the CDI and had an impact on the clinical course of their IBD.

Methods:

We conducted a retrospective review of Mayo Clinic records for pediatric IBD patients who underwent a FMT between 2013 and 2015, by colonoscopy for the purpose of treating refractory CDI. IBD medications, endoscopic findings, and laboratory results before and after FMTs were compared. Patients were contacted for an update on clinical status and medication adjustments. In order to approximate the extent of patient's IBD activity, we used Physician Global Assessment (PGA) which includes clinical status and

Lab results including albumin, WBC count, Hemoglobin, CRP, and Calprotectin.

Results:

A total of 9 patients were identified (7 males, 2 females with average age of 13.8). Five patients had Ulcerative Colitis, three had Crohn's Disease, and one had indeterminate colitis.

While it is challenging to identify which symptoms are due to CDI versus an IBD flare, all nine of the patients evaluated in this study had documented improvement of their diarrhea during antibiotics (metronidazole or vancomycin) prior to relapse which suggests that the diarrhea was related to the infection rather than the IBD. Additional lab assessments including albumin, hemoglobin, and crp were inconsistently checked in the patients leading up to FMT but are included.

Regardless of symptoms being related to CDI or IBD relapse, we evaluated patients' status using PGA prior to undergoing FMT. Results showed 2 patients having no activity, 3 with mild disease, and 4 with moderate disease activity. Lab results showed 2/7 patients had elevated CRP levels prior to FMT. At the time of the FMT, all 9 of the patients had endoscopic evidence of active inflammation.

Following FMT, all nine patients showed symptom resolution and returned to clinical baseline, which we define as the status immediately prior to acquiring CDI. This clinical improvement was attributed to CDI eradication. As shown in Table 1, four patients experienced relapse of symptoms within a month from FMT, 3 of whom were retested for stool CD toxin and were found to be negative, suggesting an early IBD relapse was responsible for the symptoms. Table 1 also lists medications used pre- and post-FMT; pre-FMT meds included maintenance and/or a trial of induction therapy. In assessment of IBD status post-FMT, eight patients had IBD relapses at some point and had a step up in their therapy. Only one patient reported no relapse and continued on maintenance therapy. None of the nine patients stopped or reduced their IBD maintenance therapy following FMT.

Patient Number	Gender	Age	IBD	Pre-FMT clinical status	IBD meds Pre-FMT	IBD meds Post-FMT	post-transplant stool C.diff	Follow-up (Physician Global Assessment, IBD medication)
1	M	16	Ulcerative Colitis	Mild disease: 7-10 bowel movements/ dark color stool	Balsalazide 750mg, Prednisone 25mg	Mesalamine		Inactive; No relapses since FMT/still on Mesalamine
2	M	17	Crohn's	Mild disease: Formed stool with occasional loose stool and some stomach pain	Azathioprine	Prednisone 40 mg and Mesalamine 2.4gm /day(2 weeks later), IV steroids and Infliximab (3 weeks later)	Negative	A week post FMT; Fever, 8 stools/day later became 12/day--- hospitalized for dehydration
3	M	12	Ulcerative Colitis	Moderate Disease: 2-3bowel movements/day with blood and mucus	(a month pre-FMT) 3rd dose of Infliximab + prednisone tapering and budesonide	20mg prednisone + started hydrocortisone enemas (1 month post FMT), hydrocortisone enema+ mercaptopurine + prednisone+ infliximab (5 months post FMT	Negative	1 month later(He has two to four bowel movements a day with some solid stool mixed with overt blood and mucus. He has urgency and tenesmus)
4	M	15	Ulcerative Colitis	No disease activity	Budesonide	Advised to start immunosuppression by adult GI but patient left for FMT trial elsewhere		Symptoms relapse 4 days later (After the fecal transplant he had several days where he felt like he was feeling quite better)
5	M	15	Ulcerative Colitis	Moderate disease: loose/semi-formed stool with nocturnal bowel movements	Prednisone	Infliximab + Prednisone taper (1.5months later)	Negative	1 week later 18 stools with blood, 3 months later- 20 stools a day

6	F	14	Ulcerative Colitis	Moderate disease: 4-6 loose stools, occasional blood in stool, abdominal cramping, low grade fever	Prednisone	Infliximab		infliximab after the FMT for bad UC activity
7	F	8	Crohn's	Mild disease: Mild diarrhea	Budesonide+Bi-weeklyAdalimumab	Budesonide+Weekly Adalimumab		increased to weekly Adalimumab post-FMT
8	M	12	indeterminant colitis	Moderate disease: loose stools with blood	Balsalazide	Started on steroids enema and suppositories	Negative	Symptom resolution for 5 months then recurred
9	M	16	Crohn's	No disease activity	Mesalamine	Budesonide (2 weeks post) mesalamine +Budesonide taper (2 months post), Humira started (3 months post FMT)		better stools until present (4 months post-FMT) except for dropped weight and lost appetite

Table 1: List of patients including Demographics and Medication changes.

Discussion:

In cases where Metronidazole and Vancomycin fail to eradicate CDI, FMT has been recognized as a successful alternative by replenishing disrupted colonic bacterial flora. Several reports indicate disruption of bacterial flora as a key factor in the pathogenesis of IBD and hypothesized the potential benefit of FMT in treating IBD patients even in the absence of a CDI [13, 14]. A 2012 review includes 13 case reports of IBD patients treated with FMT who had complete resolution of IBD symptoms within 6 weeks. Most of these were adults who had received multiple FMT enemas. Other case reports document using FMT in treating CDI in patients with underling IBD; Of these cases, 11/12 showed reduction or resolution of diarrhea, 6/7 had improved response to IBD medication, the majority of this group with both IBD and CDI received a single infusion of FMT [9]. A more recent review, which included cases mentioned above, described symptom reduction or resolution in 55/77 IBD patients, and 25/36 IBD patients with concomitant CDI [10].

Two randomized clinical trials in an adult population had contradictory results regarding the induction of remission in active cases of UC. Both studies compared outcomes in patients receiving FMT to those receiving placebo. One of these studies found FMT to be statistically significant when compared to placebo; FMT inducing remission in 9 out of 38 cases versus only 2 out of 37 cases receiving placebo. While the other study showed remissions in 7/23 receiving FMT and 5/25 on placebo, denying any statistical significance [11, 12]. On a smaller scale, two trials tried to induce remission of active UC in a pediatric population using FMT. Daily enemas for 5 consecutive days were found successful at lowering PUCAI score in 6/9 patients. While a single FMT failed to impact scores in four children receiving a FMT through nasogastric tube [15, 16].

The diversity of outcomes and methodology in these reports prompts a need for more studies designed to assess the impact of FMT on IBD, especially in the pediatric population. With the limitation of being a retrospective study, we were able to track and compare clinical, lab, and medication changes in IBD patients before and after a single FMT. Following a single FMT infusion, our results show that nine patients displayed resolution of acute diarrheal symptoms that had emerged with the CDI. Patients had insignificant PGA changes in addition to no direct alterations in IBD medications correlating to FMT. Our results corroborates an earlier series that describes no change in PGA in 3 patients following a single FMT [19]. We add that none of our 9 patients stopped IBD maintenance therapy, and 88% of patients suffered an IBD relapse at some point following FMT despite eradication of the acute diarrhea that arose from the CDI. Early IBD relapses/ IBD flares following FMT had been reported in adults [20, 21]. Interestingly, both of our patients with elevated CRP levels prior to FMT had IBD relapse within a month of FMT, with one of them getting hospitalized for dehydration. Perhaps IBD relapses could be anticipated following FMT in cases where CRP levels are high and we are investigating this question in our current prospective FMT trials.

Conclusion:

While modest in number, this group of 9 patients is one of the largest pediatric cohorts of IBD patients with concomitant CDI treated with FMT. Based on our results, we conclude that a single infusion of FMT has no major impact on IBD activity. FMT does not appear to have altered the course of the underlying disease beyond the acute treatment of the CDI. Further prospective studies are encouraged to establish the true effects of FMT on the underlying course of disease in IBD patients as our retrospective look suggests the benefits may be limited.

References

1. Lessa FC, Winston LG, McDonald LC (2015) Emerging Infections Program C difficile Surveillance Team. Burden of Clostridium difficileinfection in the United States. N Engl J Med 372: 2369-2370.
2. Khanna S1, Baddour LM, Huskins WC, Kammer PP, Faubion WA, et al. (2013) The epidemiology of Clostridium difficile infection in children: a population-based study. Clin Infect Dis 56: 1401-1406.
3. Hourigan S, Chen LA, Grigoryan Z, Laroche G, Weidner M, et al. (2015) Microbiome Changes Associated With Sustained Eradication of Clostridium difficile After Fecal Microbiota Transplantation in Children With and Without Inflammatory Bowel Disease. Gastroenterology 148: p. S45-S45.
4. Cammarota G1, Ianiro G, Gasbarrini A (2014) Fecalmicrobiota transplantation for the treatment of Clostridium difficileinfection: a systematic review. J ClinGastroenterol 48: 693-702.
5. Issa M1, Vijayapal A, Graham MB, Beaulieu DB, Otterson MF, et al. (2007) Impact of Clostridium difficile on inflammatory bowel disease. ClinGastroenterolHepatol 5: 345-351.
6. Kelsen, J.R., et al. (2011) Recurrence rate of clostridium difficile infection in hospitalized pediatric patients with inflammatory bowel disease. Inflamm Bowel Dis 17: p. 50-55.
7. Di Bella S, Gouliouris T, Petrosillo N (2015) Fecal microbiota transplantation (FMT) for Clostridium difficile infection: focus on immunocompromised patients. J Infect Chemother 21: p. 230-237.
8. Wei Y1, Zhu W1, Gong J1, Guo D1, Gu L1, et al. (2015) Fecal Microbiota Transplantation Improves the Quality of Life in Patients with Inflammatory Bowel Disease. Gastroenterol Res Pract 2015: 517-597.
9. Anderson JL, Edney RJ, Whelan K (2012) Systematic review: faecalmicrobiota transplantation in the management of inflammatory bowel disease. Alimentary pharmacology & therapeutics 36: p. 503-516.
10. Ianiro G1, Bibbò S, Scaldaferri F, Gasbarrini A, Cammarota G (2014) Fecal microbiota transplantation in inflammatory bowel disease: beyond the excitement. Medicine (Baltimore) 93: e97.
11. Moayyedi P (2015) Fecal Microbiota Transplantation Induces Remission in Patients With Active Ulcerative Colitis in a Randomized Controlled Trial. Gastroenterology 149: p. 102-109 e6.
12. Rossen NG (2015) Findings From a Randomized Controlled Trial of Fecal Transplantation for Patients With Ulcerative Colitis. Gastroenterology 149: p. 110-118 e4.
13. Allegretti JR1 and Hamilton MJ1 (2014) Restoring the gut microbiome for the treatment of inflammatory bowel diseases. World J Gastroenterol 20: 3468-3474.
14. Damman CJ1, Miller SI, Surawicz CM, Zisman TL (2012) Themicrobiome and inflammatory bowel disease: is there a therapeutic role for fecal microbiota transplantation? Am J Gastroenterol 107: 1452-1459.
15. Kunde S (2013) Safety, tolerability, and clinical response after fecal transplantation in children and young adults with ulcerative colitis. Journal of pediatric gastroenterology and nutrition 56: p. 597-601.
16. Suskind DL (2015) Fecal microbial transplant via nasogastric tube for active pediatric ulcerative colitis. Journal of pediatric gastroenterology and nutrition. 60: p. 27-29.
17. Russell GH (2015) Too early to determine whether fecal microbiota transplant has therapeutic promise for Ulcerative Colitis? Journal of Pediatric Gastroenterology & Nutrition 60: p. 3.
18. Kelly CR (2015) Update on Fecal Microbiota Transplantation 2015: Indications, Methodologies, Mechanisms, and Outlook. Gastroenterology 149: p. 223-237.
19. Russell GH (2014) Fecal transplant for recurrent Clostridium difficile infection in children with and without inflammatory bowel disease. Journal of pediatric gastroenterology and nutrition. 58: p. 588-592.
20. De Leon LM, Watson JB, Kelly CR (2013) Transient flare of ulcerative colitis after fecal microbiota transplantation for recurrent Clostridium difficile infection. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association 11: p. 1036-1038.
21. Kelly CR (2014) Fecal microbiota transplant for treatment of Clostridium difficile infection in immunocompromised patients. The American journal of gastroenterology 109: p. 1065-1071.