Successful colonoscopic fecal microbiota transplantation for active ulcerative colitis: First report from India

Avnish Kumar Seth, Pawan Rawal, Ruchika Bagga & Priti Jain

Indian Journal of Gastroenterology

ISSN 0254-8860

Indian J Gastroenterol
DOI 10.1007/s12664-016-0696-2

Springer

Indian J Gastroenterol
DOI 10.1007/s12664-016-0696-2

CASE REPORT

Successful colonoscopic fecal microbiota transplantation for active ulcerative colitis: First report from India

Avnish Kumar Seth[1] · **Pawan Rawal**[1] · **Ruchika Bagga**[2] · **Priti Jain**[2]

Received: 26 April 2016 / Accepted: 6 September 2016

Abstract Forty-four-year-old male with ulcerative colitis (UC) for 11 years reported frequent relapse despite daily sulfasalazine 4 g, azathioprine 125 mg, and rectal 5-aminosalicylic acid. Repeated use of corticosteroids led to cataract. At enrollment, he was passing eight stools a day with blood with a Mayo score of 9 (3+1+3+2). Stool was negative for ova/cysts/acid fast bacilli and Clostridium difficile toxin assay. Rectal biopsy showed cryptitis, crypt abscess, and crypt distortion with no inclusion bodies, and cytomegalovirus DNA was negative. Following informed consent and approval from IEC, three sessions of fecal microbiota transplant (FMT) were performed at intervals of 2 weeks. The donor was a 34-year-old relative with no history of gastrointestinal illness, no use of antibiotics over 3 months, and free from transmissible disease as per standard protocol. At colonoscopy, 350 mL of blended and filtered donor stool, drawn into seven syringes of 50 cm^3, was instilled from terminal ileum to sigmoid. Follow up sigmoidoscopy and rectal biopsy were done monthly for 6 months. There was symptomatic, colonoscopic, and histopathological improvement with the Mayo scores of 4.1 and 0 at 4.8 and 12 weeks post FMT. Azathioprine and sulfasalazine were tapered sequentially between months 4 and 6 of FMT. He remains in clinical and endoscopic remission 8 months after FMT and 2 months after withdrawal of all medication. Colonoscopic FMT may be effective in inducing drug-free remission in patients with active UC.

Keywords Fecal microbiota transplant · Ulcerative colitis

Introduction

Fecal microbiota transplantation (FMT) is an established indication for refractory clostridium difficile infection [1]. Dysbiosis in ulcerative colitis (UC) has been consistently demonstrated with a decrease in Firmicutes and Bacteroides and an increase in Proteobacteria and Actinobacteria as compared to healthy population [2]. However, the role of FMT in treatment of UC remains controversial [3]. We report the successful use of colonosopic FMT in a patient with UC with dependence on corticosteroids (CS) and failure to maintain remission with 5-aminosalicylates (5-ASA) and thiopurines.

Case report

Forty-four-year-old male first became symptomatic with frequent stools mixed with blood in 2004. Colonoscopy and biopsy revealed features of UC involving the rectum and sigmoid colon. He received oral CS for 4 weeks and maintained remission on 5-ASA for 2 years. He then decided to discontinue medication and did well for 7 years. In 2013, there was relapse of severe UC with sacro-iliitis requiring CS, azathioprine 125 mg, and Salazopyrin 4 g/day with topical mesalamine. Corticosteroids could not be tapered below 10 mg per day, and he went on developing adverse effects including bilateral cataract. He was counseled for FMT as a part of an open-label trial approved by the Institutional Ethics Committee. The Mayo score at the time of recruitment was 8 with colonoscopic score of 3 and extent E-2. Rectal biopsy showed cryptitis, crypt abscess, and crypt distortion with no

✉ Avnish Kumar Seth
akseth2003@yahoo.com

[1] Department of Gastroenterology and Hepatobiliary Sciences, Fortis Memorial Research Institute, Sector 44, Gurgaon, Haryana 122 002, India

[2] Department of Pathology, Fortis Memorial Research Institute, Sector 44, Gurgaon, Haryana 122 002, India

Published online: 08 October 2016

Table 1 Evaluation protocol for recipient and donor

	Recipient	Donor
Stool tests		
Ova and cysts	Yes	Yes
Modified Ziehl-Neelsen stain	Yes	Yes
Clostridium difficile toxin assay A and B by ELISA	Yes	Yes
Culture	Yes	Yes
Blood tests		
HBsAg	Yes	Yes
Anti-HCV	Yes	Yes
Human immunodeficiency virus	Yes	Yes
Cytomegalovirus DNA	Yes	–
VDRL	–	Yes
IgM anti-HAV	Yes	Yes
IgM anti-HEV	Yes	Yes

inclusion bodies. Stool was negative for Clostridium difficile toxin. Hb was 12 g/dL, CRP 7.4 mg/dL, and serum albumin 3.9 g/dL. His brother-in-law, 34 years, who consented for stool donation, had not used antibiotics within preceding 3 months and had no history of high-risk sexual behavior, use of illicit drugs, tattoo, or body piercing within 6 months. There was no history of gastrointestinal (GI) surgery, inflammatory bowel disease (IBD), irritable bowel syndrome, chronic constipation, chronic diarrhea, eosinophilic disorders, colonic polyposis, malignancy, metabolic syndrome, autoimmunity, atopic disease, chronic fatigue syndrome, or fibromyalgia. Recipient and donor assessment were carried out as per protocol mentioned in Table 1.

Three sessions of FMT were carried out at intervals of 2 weeks. Two hundred grams of fresh donor stool was blended with 300 mL of saline, strained, and 350 mL of FMT material, drawn into seven syringes of 50 cm^3, was transported on ice. The temperature of FMT material was average 15.4 °C (range 10–20.8 °C) on arrival and 30.8 °C (range 30–31.2 °C) at instillation. Colonoscopy was performed under sedation following preparation with polyethylene glycol and FMT material instilled from terminal ileum to sigmoid colon. Donation to FMT time was average 231 min (range 193 to 290 min). Post instillation, the foot end of the bed was raised and the recipient nursed in left lateral decubitus till awake and then asked to change position to supine, right lateral and prone every 15–30 min. The recipient was kept nil by mouth for 4 h and administered IV fluids and loperamide 4 mg after 30 min and 4 h of FMT. The average stool retention time was 505 min (range 138 to 797 min). There were no adverse effects. The recipient was allowed to continue medication for UC and followed up monthly with flexible sigmoidoscopy, biopsy, and Mayo scores.

Clinical response to FMT was noted within 2 weeks of first session of FMT. Complete remission with Mayo scores improving to 0 for stool frequency, blood in stool, and colonoscopy were noted at weeks 4, 8, and 12, respectively (Fig. 1). Significant histological improvement, as determined with Geboes score, was noted at 16 weeks. Azathioprine and 5-ASA were tapered, and he remains in clinical and endoscopic remission 10 months after FMT and 5 months after withdrawal of all medication. Histopathology at 10 months follow up was normal.

Discussion

Successful use of FMT for UC was first reported by Bennet in 1989 when he documented reversal of his own colitis following retention enemas from a healthy donor [4]. Suffering from steroid dependent UC of 7 years, he was asymptomatic without medication 3 months post FMT and histology revealed no active inflammation. In 2003, Borody et al. from Sydney reported six patients with UC of less than 5-year duration, all of whom achieved drug-free remission 4 months following weekly FMT enema for 5 weeks [5]. At 1- to 13-year

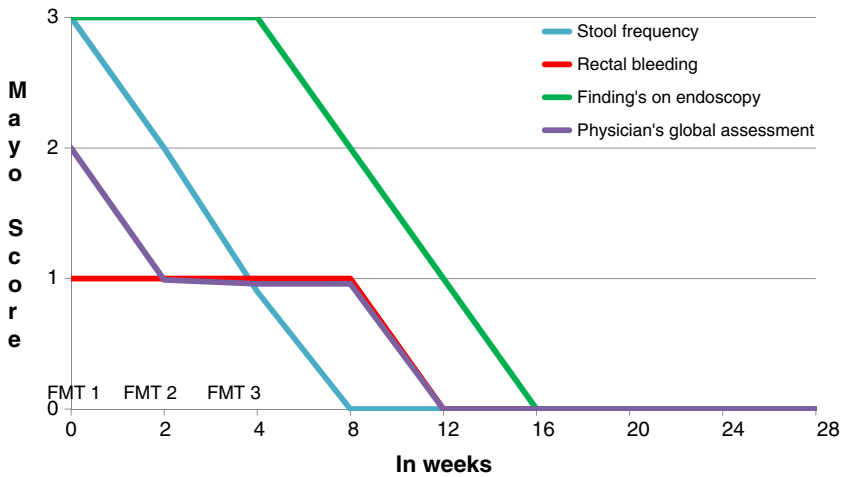

Fig. 1 Response to fecal microbiota transplant (FMT)

follow up, there was no clinical, colonoscopic, or histologic evidence of UC without any medication. A systematic review and meta-analysis of 18 studies that included 122 patients with IBD who underwent FMT found a clinical remission rate of 22 % in patients with UC [6]. Although no serious adverse events were reported, some patients experienced fever, chills, bloating, flatulence, vomiting, diarrhea, and abdominal tenderness. The adverse events were more likely with nasogastric route of administration for FMT. Flares of UC following FMT were also described. Two randomized placebo-controlled trials of FMT in IBD were recently reported [7, 8]. In the study by Moayyedi et al., patients with active UC were randomized to weekly FMT or water enema for 6 weeks. Remission (Mayo score <3 and complete mucosal healing) was achieved in 24 % of patients after FMT and 5 % with placebo; stool from patients receiving FMT had greater microbial diversity than that of patients given placebo. The second study, conducted in Amsterdam, enrolled patients with active UC and randomized them to FMT or autologous fecal transplant via a nasoduodenal tube at the start of the study and after 3 weeks. Clinical and endoscopic remission was not statistically different between the two groups (30.4 % in study group vs. a high 20 % in controls).

The factors that determine response to FMT in patients with UC are not known. The ideal patient seems to be one with active UC who is either steroid dependent (more than 10 mg per day of prednisolone) or intolerant to thiopurines. However, it has been described that patients with UC of less than 1-year duration and those on immunosuppression may respond better [7]. Whether the use of FMT early in the course of UC alters the natural history of the disease remains to be seen. The quality of donor stool seems to be an important determinant of response as "star donors" have been identified in most studies. This factor has prompted commercial availability of what is considered "ideal stool" for use in FMT through rectal or oral route and also as pills [9]. In the absence of robust data, the volume of FMT used does not appear to be of significance but most authors feel that the colonoscopic/rectal administration may be preferable and more acceptable than the nasogastric route. The use of upper GI route might render the active constituent of FMT ineffective by the time it reaches the diseased colon. We decided to use colonoscopic instillation as it is more likely to result in successful engraftment as compared to retention of rectally instilled material in a patient with frequent passage of stools. Randomized control trials with repeated colonoscopic instillation may be difficult to design and implement because of the invasive nature, use of sedation, and cost of the procedure. The ideal frequency of administration of FMT is also not clear. It has been mentioned that donor similarity index of 40 % to 50 % is required for response to FMT, and a single session of colonosopic instillation achieves the same in two thirds of the patients [10]. Dynamic behavior is an intrinsic property of fecal microbiota, and attrition of fecal microbiota to pre-FMT state is likely to begin almost immediately [11]. However, the ideal frequency of administration of FMT is unknown. It is no surprise that with so many unaccounted variables, it has been suggested that FMT for UC should remain in clinical trials and not clinical practice [12]. In the absence of a control arm, it will be difficult to differentiate between spontaneous remission of UC and role of FMT in inducing remission in our patient. However, the latter is likely in view of the temporal profile described by us and merits further studies in large randomized controlled trials.

References

1. Cammarota G, Ianiro G, Gasbarrini A. Fecal microbiota transplantation for the treatment of Clostridium Difficile infection: a systematic review. J Clin Gastroenterol. 2014;48:693–702.
2. Junjie Q, Ruiqiang L, Jeroen R, et al. A human gut microbial gene catalog established by metagenomic sequencing. Nature. 2010;464:59–65.
3. Colleen RK, Stacy K, Purna K, et al. Update on fecal microbiota transplantation 2015: indications, methodologies, mechanisms, and outlook. Gastroenterology. 2015;149:223–37.
4. Bennet JD, Brinkman M. Treatment of ulcerative colitis by implantation of normal colonic flora. Lancet. 1989;1:164.
5. Borody TJ, Warren EF, Leis S, Surace R, Ashman O. Treatment of ulcerative colitis using fecal bacteriotherapy. J Clin Gastroenterol. 2003;37:42–7.
6. Colman RJ, Rubin DT. Fecal microbiota transplantation as therapy for inflammatory bowel disease: a systematic review and meta-analysis. J Crohns Colitis. 2014;8:1569–81.
7. 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;149:102–9.
8. Rossen NG, Fuentes S, van der Spek Mirjam J. Findings from randomized controlled trial of fecal transplantation for patients with ulcerative colitis. Gastroenterology. 2015;149:110–8.
9. Petrof EO, Gloor GB, Vanner SJ, et al. Stool substitute transplant therapy for eradication of Clostridium Difficile infection: 'RePOOPulating' the gut. Microbiome. 2013;1:3.
10. Damman CJ, Brittnacher MJ, Westerhoff M, et al. Low level engraftment and improvement following a single colonoscopic administration of fecal microbiota to patients with ulcerative colitis. PLoS One. 2015;10:e0133925.
11. Weingarden A, Gonzalez A, Vazquez-Baeza Y, et al. Dynamic changes in short- and long-term bacterial composition following fecal transplantation for recurrent Clostridium Difficile infection. Microbiome. 2015;3:10.
12. Grinspan AN, Kelly CR. Fecal microbiota transplantation for ulcerative colitis: not just yet. Gastroenterology. 2015;149:15–8.