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ORIGINAL ARTICLE

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난치성, 재발성 *Clostridium difficile* 감염에서 대변세균총이식: 9예의 임상증례보고

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Fecal Microbiota Transplantation for Refractory and Recurrent *Clostridium difficile* Infection: A Case Series of Nine Patients

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Background/Aims: Fecal microbiota transplantation (FMT) is a highly effective therapy for refractory and recurrent *Clostridium difficile* infection (CDI). Despite its excellent efficacy and recent widespread use, FMT has not been widely used in South Korea thus far. We describe our experience with FMT to treat refractory/recurrent CDI.
Methods: We conducted a chart review of patients who underwent FMT for refractory/recurrent CDI at Inha University Hospital, between March 2014 and June 2016. The demographic information, treatment data, and adverse events were reviewed. FMT was administered via colonoscopy and/or duodenoscopy. All stool donors were rigorously screened to prevent infectious disease transmission.
Results: FMT was performed in nine patients with refractory/recurrent CDI. All patients were dramatically cured. Bowel movement was normalized within one week after FMT. There were no procedure-related adverse events, except aspiration pneumonia in one patient. During the follow-up period (mean 11.4 months), recurrence of CDI was observed in one patient at one month after FMT due to antibiotics.
Conclusions: FMT is a safe, well-tolerated and highly effective treatment for refractory/recurrent CDI. Although there are many barriers to using FMT, we expect that FMT will be widely used to treat refractory/recurrent CDI in South Korea. **(Korean J Gastroenterol 2017;69: 226-231)**

Key Words: Fecal microbiota transplantation; *Clostridium difficile*; Colonoscopy; Gastrointestinal microbiome

INTRODUCTION

The incidence and severity of *Clostridium difficile* infection (CDI) have been increasing worldwide.[1] Although metronidazole and oral vancomycin are effective in treating CDI, the effectiveness decreases with recurrent episodes. It is estimated that 15-20% of patients experience recurrence of CDI. After the first relapse, risk of further recurrence increases to up to 60%.[2] Patients with recurrent CDI become dependent on oral vancomycin therapy for extended periods with only temporary resolution. The therapeutic efficacy of fecal microbiota transplantation (FMT) in treating refractory/relapsing

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CDI is more than 90%.[3-5] Moreover, FMT treatment provides a lower recurrence rate[3] because the gut microbiota from the donor quickly adapts in the recipient's colon after FMT and remains healthy for an extended time.[6] Therefore, FMT is strongly recommended in European countries after the second recurrence of CDI.[7] However, despite growing interest in FMT to treat refractory/relapsing CDI, it has not been widely used in Korea. We were able to find several cases[8-10] and one case series[11] in the literature. We share our experiences of nine patients with recurrent/relapsing CDI who were successfully treated using FMT.

SUBJECTS AND METHODS

1. Subjects

We reviewed the medical records of refractory/relapsing CDI patients who underwent treatment using FMT at Inha University Hospital, between March 2014 and June 2016. All patients who were suspected of CDI received a stool test for *clostridium difficile (C. difficile)* toxin and sigmoidoscopy/colonoscopy. In this case series, a diagnosis of CDI was based on symptoms of colitis, confirmed by *C. difficile* toxin-positive stool or typical endoscopic and histologic findings that demonstrated pseudomembranous colitis.[7] A response to treatment was measured by clinical response, such as decreasing stool frequency, as well as laboratory and radiologic findings. As Inha University Hospital is a tertiary care referral center, some patients included in this case series received medical care and treatment at other medical facilities prior to receiving FMT at our institution. We made every effort to obtain the medical records and treatment course. Informed consent for FMT was obtained from all patients. This study was approved by the Institutional Review Board of Inha University Hospital.

2. Stool donor screening and FMT

Stool was donated from a family member, friend, or healthy donor. Before FMT, we asked the family of patients to select the stool donor. If a suitable stool donor was not available, we selected an unrelated donor from healthy volunteers. Potential donors were scrutinized and screened to minimize the risk of transmitting infectious diseases. Donor stool testing included ova and parasites exam, *C. difficile* toxin, Rotavirus antigen, Giardia antigen and stool culture for *Salmonella, Shigella, and Campylobacter* species. Donor blood testing included complete blood count, blood chemistry test, amoebic antibody, hepatitis A, B and C, HIV Ag/Ab, and venereal disease research laboratory.

Fresh donor stool (>50 g) was mixed with normal saline

Table 1. Demographics of the Patients

No	Sex	Age	Underlying illness	No. of CDI episode	Disease severity	Index infection	Symptom duration (day)	PMC	Antibiotic therapy before FMT (day)[a]
1	F	66	Brain tumor, CVA	1	Severe	UTI	20	No	MTZ (7) VNC (8)
2	F	70	s/p Rectal Ca	3	Severe	Acute colitis	100	Yes	MTZ (10) VNC (28)
3	M	91	CVA, bed ridden	1	Complicated	UTI	60	No	MTZ (10) VNC (55)
4	F	94	CVA, bed ridden	2	Moderate	Pneumonia	120	No	MTZ (35) VNC (50)
5	M	82	Back pain, bed ridden	1	Severe	Pneumonia	20	Yes	MTZ (8) VNC (5)
6	M	56	CVA, bed ridden	1	Severe	Pneumonia	14	Yes	MTZ (9) VNC (8)
7	M	57	None	3	Severe	Diverticulitis	60	Yes	MTZ (14) VNC (10)
8	F	55	Brain tumor complicated UTI	3	Severe	Recurrent UTI	20	Yes	MTZ (0) VNC (15)
9	M	82	Dementia, bed ridden	1	Severe	Unknown	30	Yes	MTZ (7) VNC (7)

F, female; M, male; CVA, cerebrovascular accident; UTI, urinary tract infection; PMC, pseudomembranous colitis; FMT, fecal microbiota transplantation; MTZ, metronidazole; VNC, vancomycin.
[a]Duration of antibiotics use before fecal microbiota transplantation.
Disease severity followed the criteria of Leffler and Lamont.[22]

Table 2. Technical Methods and Clinical Outcomes of FMT

No	No. of FMT	Route of FMT	Donor relationship	Stool weight (g)	Infusion volume (mL)	Adverse effects	Recurrence	Follow-up duration (month)
1	1	Lower	Daughter	50	500	None	None	12
2	1	Lower	Daughter	70	500	None	None	27
3	1	Upper	Son	50	350	Aspiration pneumonia	None	17
4	1	Lower	Daughter	50	500	None	None	13
5	1	Lower	Unrelated	50	500	None	None	17
6	1	Lower	Unrelated	80	700	None	Yes	9
7	1	Lower	Wife	50	550	None	None	4
8	1	Both	Daughter	25	500	None	None	2
9	1	Lower	Unrelated	70	700	None	None	2

FMT, fecal microbiota transplantation.

and was homogenized by stirring manually. Then thereafter, stool emulsion was filtered using a gauze or coffee filter. The filtered stool emulsion was directly infused into the gastrointestinal (GI) tract via an endoscope. The route of FMT administration varied according to the condition of patients.

RESULTS

Eleven patients who had antibiotic-associated diarrhea received FMT. However, two patients were excluded for negative for *C. difficile* toxin and equivocal endoscopic findings. The demographic and clinical data of nine patients are listed in Table 1. Four women and five men participated, and the mean age was 74.4 years. Most patients had extensive comorbidities, and were advanced in age; five patients were bed-ridden. Prior to FMT, CDI was managed with metronidazole and/or vancomycin sequentially or simultaneously. Probiotics and/or rifaximin were used in some patients. The mean number of bowel movements was 5.5±3.1 stools per day at the time of FMT. Pseudomembranous colitis was diagnosed endoscopically in six patients (66.7 %). Six patients received fecal material from their family members, and three patients received them from unrelated healthy donors.

The data regarding FMT is shown in Table 2. The mean amount of stool used was 55 g (range, 25-80 g), and the mean volume of infused stool emulsion was 530 mL (range, 350-700 mL). Seven patients received FMT via a colonoscopy. One patient (No. 3) received FMT via a duodenoscopy due to his poor general condition (unable to undergo bowel preparation). One patient (No. 8) received FMT via both duodenoscopy and colonoscopy. Because of the radiation-induced pelvic adhesion, we could not pass the endoscope at the recto-sigmoid junction. Therefore, we administered fecal emulsion to the recto-sigmoid junction and administered remnant fecal emulsion into the jejunum via a duodenoscopy.

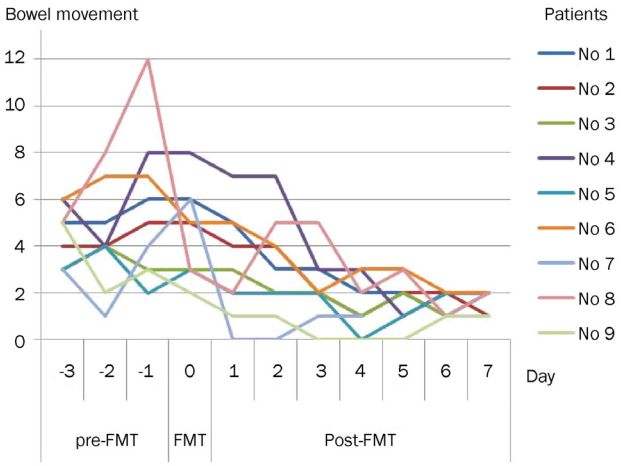

Fig. 1. Bowel movement change of before and after fecal microbiota transplantation (FMT). The mean bowel movement was 5.5±3.1 stools per day, one day prior to FMT. The mean bowel movements decreased 1.4±1.1 stools per day, at four days after FMT, and normalized within one week.

All patients showed an immediate and complete resolution of diarrhea after a single session of FMT. Bowel movement decreased to less than three per day four days after FMT and normalized within one week after FMT in all patients (Fig. 1). We also observed the improvement of pseudomembranous colitis when following-up using a colonoscopy (Fig. 2). One patient developed aspiration pneumonia after receiving FMT via a duodenoscopy. Although this patient suffered from aspiration pneumonia after FMT, his CDI dramatically improved.

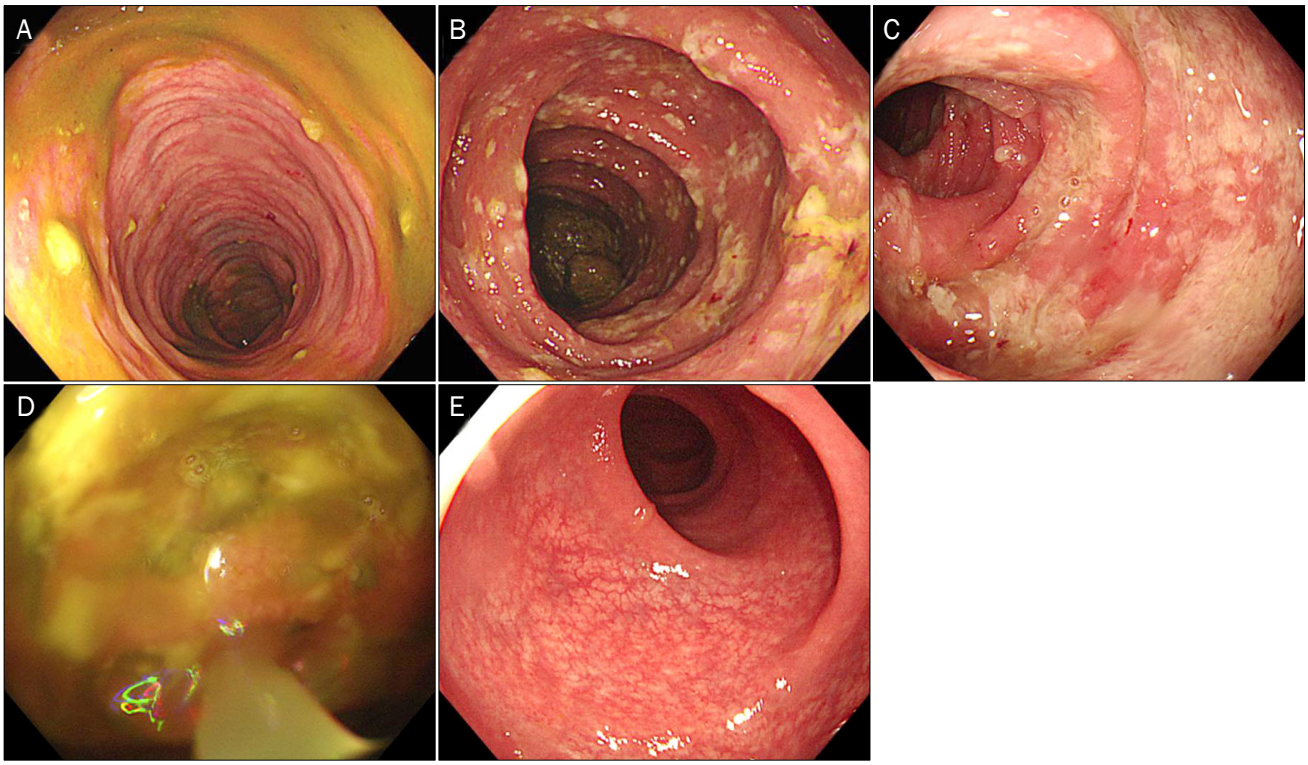

Fig. 2. Colonoscopic findings of pseudomembranous colitis. Colonoscopic finding at the time of diagnosis of pseudomembranous colitis (A), after metronidazole for 14 days (B), after vancomycin for 10 days (C), during fecal microbiota transplantation (FMT) (D) and one month after FMT (E).

When the charts were analyzed, the patients were observed for two to 23 months. One patient (No. 6) developed CDI recurrence one month post-FMT, after taking antibiotics to treat urinary tract infection. He was re-treated with oral vancomycin instead of repeated FMT.

DISCUSSION

FMT delivers a fast response and offers a cure rate of nearly 90%, with a negligible rate of significant adverse events, regardless of the administration route.[5] Moreover, it does not require a high-technology equipment and is not associated with high cost. Despite its excellent outcomes in treating refractory/relapsing CDI, it has not been widely performed in South Korea. However, we were able to find a few cases[8-10] and one case series[11] in the Korean literature. Despite minimal publications regarding the use of FMT, its acceptance appears to be growing.

There are several barriers to using FMT: 1) Concerns about infectious disease transmission, 2) aesthetic issue and patient aversion to FMT, and 3) difficulty in donor selection and screening.

First, the major concern for adopting FMT by both patients and physicians is the risk of infectious disease transmission. However, FMT should be considered safe; FMT-related infectious disease transmission has rarely been reported to date.[12] Because donor screening and testing for FMT are managed more strictly than that of blood donations, FMT should be regarded as a safer method than blood transfusion.[13] Nevertheless, evidence regarding the safety of FMT is limited, and long-term safety of FMT remains unclear. Second, we assumed that patients would refuse FMT due to aesthetic reasons. However, in our experience, most patients were willing to undergo FMT because they suffered from CDI for a long time. According to a survey, 81% of patients will choose FMT if it is necessary.[14] Therefore, aesthetics is apparently not a barrier to FMT. Third, stool donor selection and screening are very important in minimizing the risk of infectious disease transmission. However, finding a stool donor is an arduous task. In our study, when patients did not find a suitable FMT donor, we searched for healthy volunteers among hospital employees. Hospital staffs are not good candidates as stool donors because they have a high risk of nosocomial pathogen carriage. According to Openbiome, a nonprofit stool bank

in the United States, only 2.8% of candidates pass the rigorous inspection to be a stool donor. Unfortunately, there is no stool bank and specialized protocol for stool donor selection in South Korea. We hope a stool bank will be established to find healthy, prescreened and suitable donors easily soon.

Additionally, FMT techniques have not been standardized. In this retrospective study, pre-FMT management, stool preparation, infusion volume of FMT, and route of administration were determined in accordance with the preference of the clinician. Although the results of our uncontrolled study were excellent, FMT procedure regarding stool preparation, route of administration, and treatment protocols should be standardized. As the number of research regarding FMT increases, the development of a standard protocol would follow suit.[12]

In our study, all patients were successfully treated with only one session of FMT, regardless of the duration of illness prior to FMT. They had suffered from CDI for a long time, and some patients were in desperate conditions. The health burden of refractory/recurrent CDI is significant because it prolongs hospitalization, increasing the medical cost. In addition, approximately 15,000 patients die annually from CDI in the Unites States.[15] Therefore, despite our limited experience, it appears that earlier use of FMT may be important for early recovery, minimizing prolonged hospitalization. According to the European guidelines, FMT is strongly recommended after the second recurrence of CDI.[7] However, a guideline from the American College of Gastroenterology offered a more cautious recommendation: FMT should be considered after three episodes of CDI.[16]

To the best of our knowledge, the best route of FMT administration has not yet been established. In our study, all patients were successfully treated regardless of FMT route. However, aspiration pneumonia was observed in one patient who received FMT via the upper GI tract. He was bed-ridden due to cerebral hemorrhage. Although we infused fecal emulsion into the deep jejunum to avoid vomiting, he developed aspiration pneumonia. FMT via the upper GI route is easy to perform without bowel cleansing, and FMT is retained longer compared with the colonoscopic or enema route. However, vomiting and nausea are significant adverse events after FMT via the upper GI route, and it is possible for aspiration pneumonia after FMT to lead to death.[12] Therefore, FMT via the upper GI route should be performed cautiously in bed-ridden patients.

CDI recurrence was observed in a patient one month after FMT due to the antibiotics prescribed for urinary tract infection sepsis. He was readmitted into the nephrology department, where he was treated with oral vancomycin regimen instead of repeated FMT. Unlike antibiotics therapy, FMT has a low CDI recurrence rate.[3] FMT results in durable colonization of gut microbiota from the healthy donor and restores gut microbiota diversity, preventing an overgrowth of *C. difficile*.[6] However, continued use of non-*C. difficile* antibiotics is a documented risk factor for CDI recurrence.[17]

Capsulized, frozen FMT from prescreened donors was recently introduced, and it can deliver FMT orally without any loss of efficacy.[18,19] It will help overcome some practical barriers to conventional FMT, such as lag-time between donor screening and FMT, and invasive endoscopic delivery, making FMT more accessible to patients. Moreover, synthetic stool called RePOOPulate, made from purified intestinal bacterial culture, was introduced and used to treat two CDI patients successfully.[20] The exact bacterial composition is controlled, eliminating the risk of transmitting infectious diseases.[20] Besides *C. difficile* associated diarrhea, FMT has been attempted as a treatment method for dysbiosis-related diseases, such as irritable bowel disease, inflammatory bowel disease, metabolic syndrome, and many others.[5] Therefore, a different form of the next-generation FMT can be developed and applied to a broad spectrum of diseases in the near future.

Recently, fidaxomicin may be an alternative treatment for recurrent *C. difficile*, although it has not been introduced in Korea.[21,22] Fidaxomicin is a narrow spectrum antibiotic, which has been approved by the U.S. Food and Drug Administration for *C. difficile* treatment in 2011. In a comparative study with vancomycin, fidaxomicin showed similar effects to vancomycin. However, regarding the recurrence rate, fidaxomicin was 15%, while vancomycin was 25%.[21] Fidaxomicin has an extended postantibiotic effect that vancomycin does not have against *C. difficile*. However, despite the advantage of low recurrence rate compared with vancomycin, fidaxomicin has an excessively high price, making it a considerable limitation.[22]

This study has some limitations. It was a retrospective, uncontrolled study performed in a single center. Patients were treated using different pre-FMT regimens, and the use or dis-

continuation of antibiotics immediately before FMT was not controlled. The microbiota composition change before and after FMT was not analyzed. Despite the study being an uncontrolled, small case series, the effectiveness of FMT for refractory/recurrent CDI cannot be ignored.

In conclusion, FMT was determined to be a simple, safe and acceptable treatment method for CDI when traditional antibiotic therapy had proven ineffective. Although there remain many challenges regarding FMT, we hope that FMT will be widely used to treat refractory/recurrent CDI in South Korea.

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