Case Report
http://dx.doi.org/10.3947/ic.2016.48.1.31
Infect Chemother 2016;48(1):31-35
ISSN 2093-2340 (Print) · ISSN 2092-6448 (Online)

ic Infection & Chemotherapy

Fecal Transplantation using a Nasoenteric Tube during an Initial Episode of Severe *Clostridium difficile* Infection

Yong Duk Jeon[1], Namki Hong[1], Jung Ho Kim[1], Se Hee Park[1], Sung Bae Kim[1], In Ji Song[1], Hea Won Ann[1], Jin Young Ahn[1], Sun Bean Kim[1], Nam Su Ku[1,2], Kyungwon Lee[3], Dongeun Yong[3], June Myung Kim[1,2], and Jun Yong Choi[1,2]

Departments of [1]Internal Medicine, [2]AIDS Research Institute, and [3]Laboratory Medicine, Yonsei University College of Medicine, Seoul, Korea

The incidence of *Clostridium difficile* infection is increasing worldwide, and its severity and resulting mortality are also on the rise. Metronidazole and oral vancomycin remain the treatments of choice, but there are concerns about treatment failure and the appearance of resistant strains. Furthermore, antibiotic therapy results in recurrence rates of at least 20%. Fecal transplantation may be a feasible treatment option for recurrent *C. difficile* infection; moreover, it may be an early treatment option for severe *C. difficile* infection. We report a case of severe *C. difficile* infection treated with fecal transplantation using a nasoenteric tube during an initial episode. This is the first reported case of fecal transplantation using a nasoenteric tube during an initial episode of *C. difficile* infection in Korea.

Key Words: Fecal transplantation; Fecal microbiota; *Clostridium difficile*; Nasoenteric tube

Introduction

The incidence, severity, and resulting mortality of *Clostridium difficile* infection are increasing worldwide [1-3]. In spite of the considerable increase in the incidence and severity of *C. difficile* infection, metronidazole and oral vancomycin remain the treatments of choice [4]. Metronidazole is generally used for mild and moderate *C. difficile* infection, but treatment failure is a growing problem. Vancomycin is costly, and there is concern about the appearance of resistant strains [5]. Furthermore, antibiotic therapy has recurrence rates of at least 20%, which increase with each subsequent *C. difficile* infection [6]. Els van Nood et al. reported that in patients with recurrent *C. difficile* infection, fecal transplantation resulted in better treatment outcomes compared with conventional antibiotic treatment. Fecal transplantation had a cure rate of 81.3% following a single nasoenteric infusion and 93.8% following a second infusion, while standard vancomycin therapy with or without

Received: August 11, 2014 **Revised:** September 17, 2014 **Accepted:** September 17, 2014
Corresponding Author : Jun Yong Choi, MD, PhD
Department of Internal Medicine, Yonsei University College of Medicine,
50 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel: +82-2-2228-1974, Fax: +82-2-393-6884, E-mail: seran@yuhs.ac

bowel lavage had a 23.1-30.8% cure rate [7]. Fecal transplantation may be a treatment option for recurrent *C. difficile* infection; moreover, it may be an early treatment option for severe *C. difficile* infection [8]. In Korea, two cases of severe refractory *C. difficile* infection treated with fecal transplantation during an initial episode have been reported. One case used esophagogastroduodenoscopy (EGD) while the other case used enema [9, 10]. Here, we report the first case of severe initial *C. difficile* infection, refractory to antibiotics, that was treated with fecal transplantation using a nasoenteric tube in Korea.

Case Report

A 65-year-old man visited the emergency room with a 3-day history of bilateral leg weakness and fever. His blood pressure was 86/43 mmHg, and his body temperature was 39.3°C at presentation. He had a history of hypertension and recent surgery for lumbar spinal stenosis three months before admission. Initial peripheral blood count showed a white blood cell count of 4,710/mm^3 (neutrophils, 92.2%; lymphocytes, 5.2%; monocytes, 1.4%), hemoglobin level of 11.3 g/dL and platelet count of 137,000/mm^3. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) were 13.2 sec and 34.8 sec, respectively, and C-reactive protein level was 286.06 mg/L. Blood chemistry showed a total protein level of 5.1 g/dL, albumin level of 2.9 g/dL, total bilirubin level of 0.5 mg/dL, aspartate aminotransferase/alanine aminotransferase 27/17 IU/L, BUN/Cr 56.6/2.42 mg/dL, Na/K 138/4.1 mEq/L and Ca/P 7.6/2.7 mg/dL. Lumbar magnetic resonance imaging (MRI) was performed and revealed infective spondylitis and multiple paraspinal abscesses. The patient received empiric intravenous antibiotic treatment with 2.0 g ceftriaxone every 24 hours and 200 mg teicoplanin every 24 hours after peripheral blood culture and urine culture. He underwent incision and drainage of multiple abscesses. *Streptococcus intermedius* was identified in all three initial blood cultures, and the minimal inhibitory concentration (MIC) for penicillin G was 0.016 μg/mL. Antibiotics were changed to 4 million units penicillin G every 4 hours. On the 35th hospital day, he had urinary tract infection and bacteremia from an extended-spectrum beta-lactamase (ESBL) organism and was treated with 500 mg imipenem every 6 hours.

On the 59th hospital day, during conservative treatment for infective spondylitis, the patient developed a fever of 38.1°C and diarrhea**;** his blood pressure was 89/58 mmHg. Due to suspicion of *C. difficile* infection, oral 500 mg metronidazole was given every 8 hours empirically. Stool *C. difficile* toxin A/B and culture were confirmed to be positive. On the 60th hospital day, laboratory results revealed a white blood cell count of 39,560/mm^3 (neutrophils, 89.4%; lymphocytes, 6.2%; monocytes, 2.8%), hemoglobin level of 11.8 g/dL, platelet count of 292,000/mm^3, BUN/Cr of 18.0/0.65 mg/dL, and albumin level of 1.8 g/dL. On the 61st hospital day, oral metronidazole was switched to 250 mg oral vancomycin every 6 hours due to increased severity of diarrhea and the detection of paralytic ileus on abdominal X-ray despite administration of oral metronidazole. Intravenous metronidazole (every 8 hours) and vancomycin enema 500 mg (every 6 hours) were also added to the treatment course. Unfortunately, symptoms did not improve, and disseminated intravascular coagulation (DIC) progressed although leukocytosis was improved. On the 74th hospital day, laboratory results showed a white blood cell

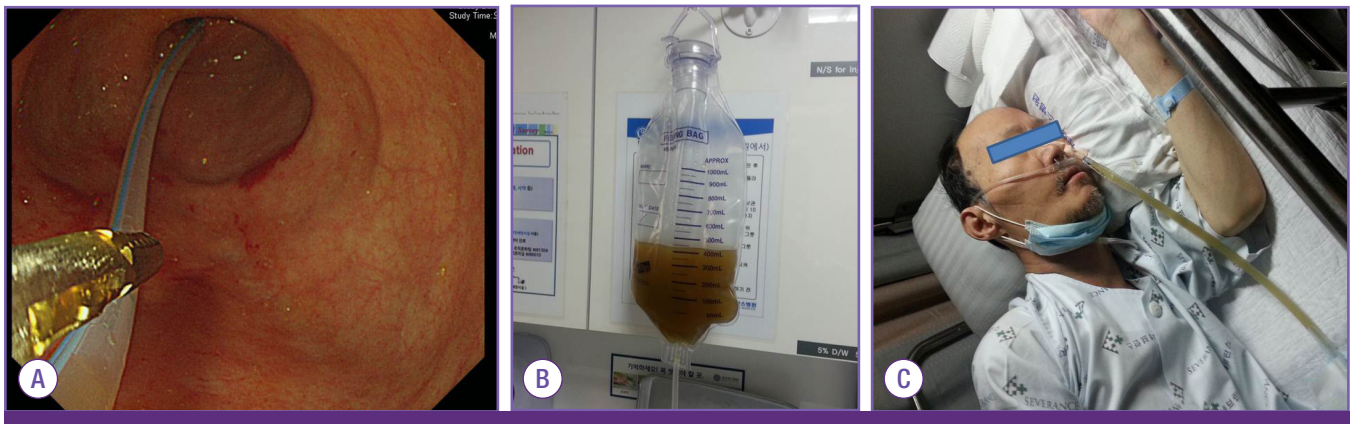

Figure 1. Method of fecal transplantation. (A) The tip of the nasoenteric tube was placed at the third portion of the duodenum by esophagogastroduodenoscopy. (B, C) Fifty grams stool collected from the donor was diluted with 500 mL normal saline, and the supernatant was filtered out with gauze. This solution was placed into the feeding bag and infused through a nasoenteric tube for 30 minutes.

count of 3,240/mm^3 (neutrophils, 71.0%; lymphocytes, 20.1%; monocytes, 6.8%), a hemoglobin level of 7.8 g/dL, platelet count of 67,000/mm^3, PT/aPTT of 22.6 sec/65.4 sec, albumin level of 1.9 g/dL and C-reactive protein level of 77.2 mg/L. Fecal transplantation was recommended and the patient consented to the procedure. The patient's wife, who had no relevant medical history and no symptoms of acute disease, was selected as the donor. On the 75th hospital day, fecal transplantation was performed. The tip of a nasoenteric tube was placed in the third portion of the duodenum by EGD. Fifty grams of stool collected from the donor was diluted with 500 mL normal saline and the supernatant was filtered out with gauze. This solution was placed into the feeding bag and infused through a nasoenteric tube for 30 minutes (Fig. 1).

After fecal transplantation, diarrhea and ileus gradually improved and fever subsided. Platelet count, PT/aPTT and albumin level were also improved (Fig. 2). On the 84th hospital day, 9 days after fecal transplantation, laboratory test results were as follows: white blood cell count 6,280/mm^3 (neutrophils, 65.3%; lymphocytes, 24.2%; monocytes, 5.3%), hemoglobin 8.1 g/dL, platelets 224,000/mm^3, PT/aPTT 14.8 sec/34.4 sec and albumin 2.7 g/dL. The patient's diet was slowly advanced, and oral vancomycin was tapered to 125 mg every 12 hours. On the 94th hospital day, the patient was discharged with oral vancomycin after his symptoms had resolved. When he visited outpatient clinic 12 days after discharge, he had no symptoms of PMC; therefore, oral vancomycin was discontinued.

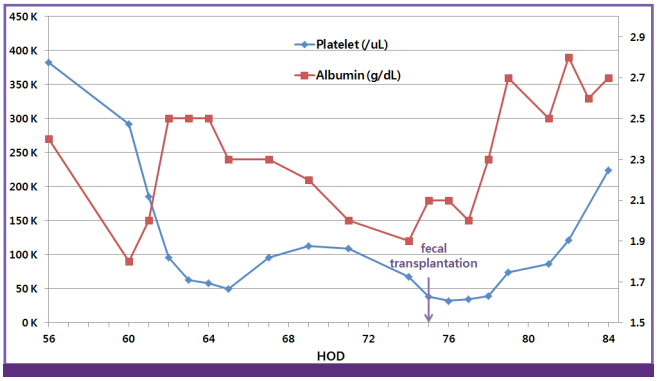

Figure 2. Serum albumin level and platelet count during treatment.
HOD, hospital day.

Discussion

The destruction of normal intestinal flora after antibiotic use is the likely cause of most *C. difficile* infections. Stool transplantation may replace the lost flora with bacteria collected from healthy donors. Reestablishment of normal gut flora makes fecal transplant a logical treatment option for *C. difficile* infection [6]. Els van Nood et al. reported that the decreased microbial diversity of infected patients recovered to the level of the donors after fecal transplantation [7].

In current clinical practice, fecal transplantation is indicated for recurrent *C. difficile* infection and severe infection with no response to standard antibiotic therapy [11]. The efficacy of fecal transplantation in recurrent *C. difficile* infection has been established in many case reports and meta-analyses and one recent randomized controlled study [12]. There is a lack of data supporting fecal transplantation use in severe or fulminant *C. difficile* infection, but emerging data indicate that fecal transplantation is also effective in such cases [8]. One recent retrospective study reported the effectiveness of fecal transplantation in 14 patients with severe, refractory *C. difficile* infection. Patients were categorized as having severe *C. difficile* infection if they met two or more of the following criteria: age

Table 1. Cases of fecal transplantation in Korea

Author (year)	Indication	Sex	Age	Donor relationship	Infusion route	Infusion volume	Outcome	Adverse events
Gweon et al. 2013 [9]	Refractory CDI	Male	83	Wife	EGD	Stool 150 g Normal saline 300 mL	CDI resolved	None
	Recurrent CDI	Male	86	Daughter	EGD	Stool 100 g Normal saline 300 mL	CDI resolved	Vomiting
Moon et al. 2013 [10]	Recurrent CDI	Male	83	Daughter	Enema	Stool 50 mL Normal saline 200 mL	CDI resolved	Mild diarrhea
	Refractory CDI	Female	70	Son	Enema	Stool 50 mL Normal saline 300 mL	CDI resolved	None
This case	Refractory CDI	Male	65	Wife	Nasoenteric tube	Stool 50 g Normal saline 500 mL	CDI resolved	None

CDI, *Clostridium difficile* infection; EGD, esophagogastroduodenoscopy.

> 60 years, serum albumin < 2.5mg/dL, body temperature > 38.3°C, or a white blood cell count > 15,000/mm^3 within 48 hours of diagnosis; or if they met one of the following criteria: endoscopic evidence of pseudomembranous colitis or treatment in the intensive care unit for *C. difficile* infection. Refractory infection was defined as non-resolution of *C. difficile* infection despite 7 days of therapy with oral vancomycin. The cure rate was 79% (11 of 14). This study included six patients with initial episodes of *C. difficile* infection [13]. Because of its cost effectiveness, high cure rate, minimal risk and reestablishment of normal flora, fecal transplantation has even been proposed as the initial treatment modality for severe *C. difficile* infection [14].

In Korea, four cases of fecal transplantation have been reported (Table 1). Two cases were recurrent *C. difficile* infections, and the other two cases were refractory *C. difficile* infections. Two cases used EGD and infused stool via the biopsy channel of EGD. The other two cases used enema. In all four cases, *C. difficile* infection resolved. Two patients had adverse events. One patient who received EGD experienced vomiting, and another patient who received enema had mild diarrhea after fecal transplantation. In our case, we used a nasogastric tube placed in the third portion of the duodenum by EGD to perform the fecal transplantation. The patient had no adverse events and recovered from *C. difficile* infection.

Fecal transplantation can be performed using a nasogastric tube, nasoenteric tube, EGD, colonoscopy, flexible sigmoidoscopy, or enema [12]. Two review studies compared fecal transplantation outcomes based on the route of administration of donor feces. One systematic review reported that fecal transplantation by EGD or nasoenteric tube had a lower resolution rate than that by colonoscopy and enema (76.4% vs > 88.7%). Most patients received treatment or preparation before fecal transplantation; therefore, estimating the effect of fecal transplantation alone was difficult [15]. The other review study compared colonoscopic fecal transplantation with nasogastric fecal transplantation from 12 published studies. Colonoscopic fecal transplantation had a superior resolution rate (93.2%) compared with nasogastric fecal transplantation (85.3%), but the difference was statistically nonsignificant [16]. There has been no randomized, controlled trial comparing outcomes based upon the route of administration of fecal transplantation. Further investigation is required to determine which route of administration is best.

Some adverse events were reported. Transient GI symptoms are common, including decreased bowel movement, abdominal cramping, increased bowel sounds and abdominal discomfort. In fecal transplantation via the upper gastrointestinal tract, the risks of aspiration and vomiting should be considered. The colonoscopic approach could be dangerous in patients with severe colitis or colonic distension [12]. A randomized controlled study by Els van Nood et al. reported acute adverse events including diarrhea (94%), cramping (31%) and belching (19%) in nasoenteric infusion, but these symptoms improved within 3 hours [7]. Long-term adverse events are not well known and require further investigation [8].

This case had one major limitation. Generally, oral vancomycin is stopped before fecal transplantation; however, oral vancomycin was continued and tapered in our case due to concerns regarding the potential failure of fecal transplantation. This could make it difficult to estimate the effect of fecal transplantation alone. Nevertheless, we are confident that fecal transplantation resulted in the resolution of *C. diffcile* infection because the patient exhibited no improvement during the previous 14 days of oral vancomycin therapy, but recovered dramatically after fecal transplantation.

In conclusion, fecal transplantation could be a viable treatment option not only for recurrent *C. difficile* infection, but also for severe initial infection. Further investigation is required to establish the optimal method of fecal transplantation and to ensure long-term safety.

Acknowledgment

This work was supported by the BioNano Health-Guard Research Center funded by the Ministry of Science, ICT & Future Planning (MSIP) of Korea as a Global Frontier Project (Grant Number H-GUARD_2013M3A6B2078953). And a grant from the Ministry of Health & Welfare, Republic of Korea (grant number: HI14C1324).

ORCID

Yong Duk Jeon http://orcid.org/0000-0002-4588-4781
Jun Yong Choi http://orcid.org/0000-0002-2775-3315

References

1. Pépin J, Valiquette L, Alary ME, Villemure P, Pelletier A, Forget K, Pépin K, Chouinard D. *Clostridium difficile*-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. CMAJ 2004;171:466-72.
2. Loo VG, Poirier L, Miller MA, Oughton M, Libman MD,

Michaud S, Bourgault AM, Nguyen T, Frenette C, Kelly M, Vibien A, Brassard P, Fenn S, Dewar K, Hudson TJ, Horn R, René P, Monczak Y, Dascal A. A predominantly clonal multi-institutional outbreak of *Clostridium difficile*-associated diarrhea with high morbidity and mortality. N Engl J Med 2005;353:2442-9.

3. Muto CA, Pokrywka M, Shutt K, Mendelsohn AB, Nouri K, Posey K, Roberts T, Croyle K, Krystofiak S, Patel-Brown S, Pasculle AW, Paterson DL, Saul M, Harrison LH. A large outbreak of *Clostridium difficile*-associated disease with an unexpected proportion of deaths and colectomies at a teaching hospital following increased fluoroquinolone use. Infect Control Hosp Epidemiol 2005;26:273-80.
4. Kelly CP, LaMont JT. *Clostridium difficile*--more difficult than ever. N Engl J Med 2008;359:1932-40.
5. Rineh A, Kelso MJ, Vatansever F, Tegos GP, Hamblin MR. *Clostridium difficile* infection: molecular pathogenesis and novel therapeutics. Expert Rev Anti Infect Ther 2014; 12:131-50.
6. Borody TJ, Paramsothy S, Agrawal G. Fecal microbiota transplantation: indications, methods, evidence, and future directions. Curr Gastroenterol Rep 2013;15:337.
7. van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, Visser CE, Kuijper EJ, Bartelsman JF, Tijssen JG, Speelman P, Dijkgraaf MG, Keller JJ. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. N Engl J Med 2013;368:407-15.
8. Borody TJ, Peattie D, Kapur A. Could fecal microbiota transplantation cure all *Clostridium difficile* infections? Future Microbiol 2014;9:1-3.
9. Gweon TG, Choi MG, Lee SK, Ha JH, Kim EY, Go BS, Kim SW. Two cases of refractory Pseudomembranous colitis that healed following fecal microbiota transplantation. Korean J Med 2013;84:395-9.
10. Moon KR, Sohn KM, Park BM, Kim YS, Chun S, Jung H, Song CH. Successful fecal transplantation by enema for recurrent and refractory *Clostridium difficile* infection. J Korean Geriatr Soc 2013;17:152-6.
11. McCune VL, Struthers JK, Hawkey PM. Faecal transplantation for the treatment of *Clostridium difficile* infection: a review. Int J Antimicrob Agents 2014;43:201-6.
12. Brandt LJ, Aroniadis OC. An overview of fecal microbiota transplantation: techniques, indications, and outcomes. Gastrointest Endosc 2013;78:240-9.
13. Zainah H, Hassan M, Shiekh-Sroujieh L, Hassan S, Alangaden G, Ramesh M. Intestinal microbiota transplantation, a simple and effective treatment for severe and refractory *Clostridium difficile* infection. Dig Dis Sci 2015;60: 181-5.
14. Brandt LJ, Borody TJ, Campbell J. Endoscopic fecal microbiota transplantation: "first-line" treatment for severe *Clostridium difficile* infection? J Clin Gastroenterol 2011;45: 655-7.
15. Gough E, Shaikh H, Manges AR. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent *Clostridium difficile* infection. Clin Infect Dis 2011;53:994-1002.
16. Postigo R, Kim JH. Colonoscopic versus nasogastric fecal transplantation for the treatment of *Clostridium difficile* infection: a review and pooled analysis. Infection 2012;40: 643-8.