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ORIGINAL ARTICLE

Long-term durability and safety of fecal microbiota transplantation for recurrent or refractory *Clostridioides difficile* infection with or without antibiotic exposure

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Abstract

Fecal microbiota transplant (FMT) is a safe and effective treatment for recurrent or refractory *Clostridioides* (*Clostridium*) *difficile* infection (RCDI) in the short term. However, there are a paucity of data on long-term durability and safety of FMT. The aim of this study is to determine the long-term efficacy and safety of FMT for RCDI. Ninety-four patients underwent FMT via retention enema for RCDI between 2008 and 2012 and completed a follow-up questionnaire 4 to 8 years following the last FMT. Of these, 32 were unreachable and 37 were deceased; 23 of the remaining 25 participants completed the survey. No CDI recurrences were reported in patients treated with FMT; 12 of the 23 participants (52.2%) received at least one course of non-CDI antibiotic(s). Nine participants (40.9%) received probiotics and 4 (17.4%) received both non-CDI antibiotics and probiotics. All 23 participants rated their overall health compared with pre-FMT. Current health was considered "much better" in 17 patients (73.9%); "somewhat better" in 3 patients (13.0%); and "about the same" in 3 patients (13.0%). A total of 11 participants (47.8%) reported an increase in weight of more than 5 kg (kg) post-FMT and 9 participants (39.1%) reported no change in weight (± 5 kg). Four of the 23 participants (17.4%) reported improvement or resolution (undifferentiated colitis, $n = 1$; Crohn's disease, $n = 2$; ulcerative colitis, $n = 1$) of pre-existing gastrointestinal condition following FMT. Eight of 23 participants (34.8%) experienced new medical condition(s) post-FMT. The long-term efficacy (48–96 months) of FMT for RCDI appears to be durable even after non-CDI antibiotic use. Thirty percent had improvement of their pre-existing medical conditions following FMT; 73.9% reported "much better" overall health following FMT.

Keywords Long-term follow-up · Fecal microbiota transplantation · Recurrent *Clostridioides difficile* infection

Introduction

Clostridioides difficile infection (CDI) represents a significant burden to the system with costs of $4.8 billion per year in the USA [1, 2]. The annual incidence of multiple recurrence (RCDI) has increased by 188.8% between 2001 and 2012 [3–5]. Fecal microbiota transplantation (FMT) is increasingly used for RCDI due to the limited efficacy of the standard antibiotics. Randomized controlled trials (RCTs) and cohort studies showed FMT to be safe with an average cure rate of 91% for RCDI [6, 7]. However, there are a paucity of long-term data on the safety and durability FMT. Published studies report a mean follow-up of a few weeks to 2 years post-FMT [8–13]. To our knowledge, our study represents the longest follow-up with a 6-year mean follow-up post-FMT.

Methods

This study was conducted at a tertiary care (St. Joseph's Healthcare, Hamilton, Canada). We contacted 94 RCDI patients treated with one or more FMT via enema. Their clinical

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outcomes at 6 to 24 months were previously reported in our retrospective study [8].

The participants completed the Table 1 questionnaire. Patients who were deceased or unreachable were excluded. The data collected from the participants was analyzed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Participant characteristics

Of the 94 patients treated, 37 (39.8%) were deceased, and 32 (34.0%) were unreachable by phone after three attempts (Table 2). Eight died due to multiple comorbidities during the 6 to 24-month follow-up [8]. The cause of death of 29 patients remained unknown, but all died at least 6 months post-FMT. 23/25 (92.0%) of participants returned questionnaires. The respondents were 15 females (65.2%; age range 28–93 years) and 8 males (34.8%; age range 54–96 years).

Long-term efficacy of fecal microbiota transplantation in participants with or without antibiotics use

23/23 (100%) of the participants reported no new episodes of CDI. Twelve participants (52.2%) received at least 1 course of antibiotic for non-CDI infection post-FMT. 10/12 participants received antibiotics for: urinary tract infection ($n = 3$), unknown but non-gastrointestinal tract ($n = 2$), tooth infection and appendicitis ($n = 1$), surgical prophylaxis for kidney transplantation ($n = 1$), pneumonia ($n = 1$), sinusitis ($n = 1$), and cellulitis ($n = 1$). 9/23 (39.1%) received probiotics for 2 weeks to 72 months.

Impact of fecal microbiota transplantation on participant health status and weight

Overall health of 23 participants (100%) was reported as fair to excellent (see Table 3): 5 (21.7%) excellent, 7 (30.4%) very good, 8 (34.8%) good, and 3 (13.1%) fair. Current health compared with health immediately following FMT was reported as: 17 (73.9%) much better, 3 (13.0%) somewhat better, 3 (13.0%) about the same, and none reported somewhat worse or much worse (Table 3).

Eleven of 23 (47.8%) participants reported weight gain > 5 kg (kg), 10 (43.5%) reported ± 5 kg, and 2 (8.6%) reported > 5 kg reduction (Table 3). Participants' weight gain ranged from 6 to 19 kg, while weight loss ranged from 9 to 20 kg.

Impact of fecal microbiota transplantation on pre-existing or new medical conditions

7/23 participants (30.4%) reported resolution or improvement of their pre-existing conditions: undifferentiated colitis ($n = 1$); Crohn's disease ($n = 2$); ulcerative colitis ($n = 1$); type 2 diabetes mellitus ($n = 1$, discontinued oral hypoglycemic); Parkinson's disease ($n = 2$, improved mobility). 8/23 (34.8%) reported diagnosis of new medical conditions after FMT, as shown in Table 3, but none developed IBD. One participant developed rheumatoid arthritis (RA) several years after the FMT.

Discussion

Our results demonstrate the long-term durability of FMT in patients with RCDI. In our previous study, none of the patients cured with FMT had RCDI at 6 to 24 months follow-up [8]. Similarly, the participants had no reported RCDI at 48 to 96 months post-FMT including 52.2% of patients who received non-CDI antibiotics following FMT. This is consistent with previously reported studies [9, 10].

In contrast, a recent study demonstrated that 18% of participants after FMT had RCDI (median 22 months), with recurrences more common with non-CDI antibiotic use [11]. Another demonstrated that 10/58 patients who received non-CDI antibiotics after FMT had a threefold increase of RCDI (mean 62 weeks; antibiotics vs. non-antibiotics, 17.2% vs. 6.4%; odds ratio (OR) 2.95; 95% CI 1.04–8.39) [12]. The authors reported that 50% of the antibiotic users also received prophylactic probiotics, with a corresponding OR of 1.63 (95% CI, 0.41–6.52); however, this association did not reach significance. In our study, 4 participants (17.4%) received both non-CDI antibiotics and probiotics after FMT. A systematic review and meta-analysis of 31 RCTs suggests moderate evidence that probiotics are effective for preventing CDI with a CDI baseline risk > 5% but not among trials with a baseline risk ≤ 5% [14]. In our study, the use of probiotics cannot be inferred as protective due to the small sample size.

Our study demonstrates the positive effect of FMT on a patient's perceived health and on their weight. Current health was reported to be better than prior to FMT in 87% of the participants. This observation may be partly explained by the lack of CDI recurrence. Approximately 91% reported that their weight stayed "about the same" or "increased." Weight gain may indicate efficacy of FMT, because weight loss and abdominal pain are CDI symptoms [10]. In a previous study, 3 of 4 CDI patients with failure to thrive (4/29, 14%) improved considerably within 1 month of FMT [9]. Although the relationship between the gut microbiota and obesity has not been fully elucidated in humans, animal models have demonstrated the transferability of obesity phenotypes through gut

Table 1 Questions regarding fecal microbiota transplantation for *Clostridium difficile* infection

1. In general, how has your overall health been since the fecal transplant?
a. Excellent b. Very good c. Good d. Fair e. Poor
2. Please rate your health now compared to your health just after the fecal transplant?
a. Much better now compared to just after the fecal transplant
b. Somewhat better now compared to just after the fecal transplant
c. About the same now compared to just after the fecal transplant
d. Somewhat worse now compared to just after the fecal transplant
e. Much worse now compared to just after the fecal transplant
3. Since the fecal transplant, has there been any significant change in your weight?
a. Increased b. About the same c. Decreased
4. What is your current weight? _____kg/Ibs
5. What was your weight around the time of the fecal transplant? _____kg/Ibs
6. Since the fecal transplant, have you been on any antibiotics?
a. Yes b. No
7. If you answered "Yes" to Question 6, please list the antibiotic(s), how long you had been on the antibiotic(s) for, and for which infection(s). _____
8. Since the fecal transplant, have you started taking any probiotic(s)?
a. Yes → If so, for how long? _____ b. No
9. Since the fecal transplant, have you started any other medication(s) and/or vitamin(s)?
a. Yes b. No
10. If you answered "Yes" to Question 9, please list the medication(s) and/or vitamin(s) and the dosage and frequency of each. _____
11. Since the fecal transplant, have you experienced any new episodes of *Clostridium difficile* infection?
a. Yes b. No
12. If you answered "Yes" to Question 11, please list when and how the episode(s) was/were treated.
_____
13. Since the fecal transplant, have you developed any new medical condition(s), such as:
a. Irritable bowel syndrome b. Cancer c. Diabetes d. Heart disease
e. High blood pressure f. Arthritis (such as rheumatoid, lupus)
g. Other condition due to "autoimmune" h. Other
14. Since the fecal transplant, has there been any resolution or improvement of any medical conditions you had prior to the fecal transplant, such as:
a. Irritable bowel syndrome b. Diabetes c. Parkinson's d. Arthritis
e. Other autoimmune condition f. Other

microbiota [15, 16]. A case report of weight gain following FMT was described; however, there was likely a genetic component with a first degree relationship between the donor and recipient [17]. All donors used in our study have BMI <

Table 2 Patients who could be contacted, or were unreachable and had the questionnaires

	Number (%)
Sent by email or mail	25 (26.6)
Passed away	37 (39.4)
Wrong number/number not in service	28 (29.8)
Not enough information to find contact info	2 (2.1)
No answer when called	2 (2.0)
Total	94
Returned	23 (24.5)

25. Although 2 participants (8.6%) showed decreased weight, we believe that this did not have a clear association with the long-term efficacy of FMT because of underlying diseases ($n = 1$, heart disease; $n = 1$, CD and RA).

Available long-term data on FMT-related AEs are limited. According to recent systematic reviews, serious AEs (infection, intestinal perforations, IBD flares, CDI, and death) have been reported at 9.2% [18, 19]. We do not believe that the deaths of any of the 37 participants can be directly attributable to FMT, because a recent review reported that all patients who died from FMT-related causes died within several days of treatment whereas the deaths of our participants occurred at least 6 months post-FMT [18].

Table 3 Post fecal microbiota transplantation outcomes

Total number of patients	23
Total number of CDI recurrences	0 (0%)
Medications	
Antibiotics for non-CDI infections	12 (52.2%)
Probiotics	9 (39.1%)
Excellent	5 (21.7%)
Very Good	7 (30.4%)
Good	8 (34.8%)
Fair	3 (13.1%)
Poor	0 (0%)
Current health compared with health at time of FMT	
Much better now	17 (73.9%)
Somewhat better now	3 (13.0%)
Same	3 (13.0%)
Somewhat worse	0 (0%)
Much worse	0 (0%)
Weight	
Increased (+ 5 kg)	11 (47.8%)
Same (± 5 kg)	10 (43.5%)
Decreased (− 5 kg)	2 (8.7%)
New significant medical condition	
Breast cancer (mastectomy only)	1 (4.3%)
Osteoarthritis of knee (hemiarthroplasty)	1 (4.3%)
Stage 4 osteoporosis	1 (4.3%)
Transient ischemic attack	1 (4.3%)
Rheumatoid arthritis	1 (4.3%)
Hypertension	1 (4.3%)
Irritable bowel syndrome	2 (8.7%)

*A participant can select multiple answers

IBD flares following FMT in patients with IBD have been reported in a meta-analysis with a pooled rate of 4.6% (95% CI, 1.8–11.0%) [20]. This is likely due to a disproportionate host immune response from the exposure to novel microbiota after FMT [20]. However, approximately 17% of participants experienced resolution or improvement of their pre-existing gastrointestinal conditions after FMT, including IBD (CD, $n = 2$; UC, $n = 1$) and undifferentiated "colitis" symptoms ($n = 1$). None of these patients experienced IBD flares.

Of the participants, 34.8% reported newly developed medical conditions although none could be directly attributed to FMT. One patient developed rheumatoid arthritis, and there are reports of possible association between FMT and the development of autoimmune disorders, although none of our donors had underlying chronic illness [10]. One case of IBS in the follow-up period was also noted, though it was likely related to post-infectious IBS following CDI [21].

Our study is limited by small sample size and single-center design. Despite these limitations, the reported durability of FMT for RCDI and its long-term safety at a 6-year mean follow-up are noteworthy.

In conclusion, this study highlights the durability of FMT in patients with RCDI, even with non-CDI antibiotic use. There were no significant long-term AEs attributable to FMT and approximately 30% of participants had improvement of pre-existing medical conditions, including IBD. FMT may have contributed to improvement in patients' perceived health in 87% of the participants.

Compliance with ethical standards

Conflict of interest CL received grants from Physicians Services Incorporated, Canadian Institutes of Health Research, Rebiotix and Seres Therapeutics to conduct fecal microbiota transplant trials. JC, KH, SRJ, YP, CG, and PK have no conflicts to declare.

Ethical approval This study was approved by the Hamilton Integrated Research Ethics Board. An informed consent was obtained from eligible participants prior to distributing the questionnaire.

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