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Is Frozen Fecal Microbiota Transplantation as Effective as Fresh Fecal Microbiota Transplantation via Colonoscopic Versus Nasogastric Tube Administration in Treating Adults with Clostridium Difficile Infection?

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Is frozen fecal microbiota transplantation as effective as fresh fecal microbiota transplantation via colonoscopic versus nasogastric tube administration in treating adults with Clostridium difficile infection?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not "is frozen fecal microbiota transplantation as effective as fresh fecal microbiota transplantation via colonoscopic versus nasogastric tube administration in treating adults with Clostridium difficile infection?"

STUDY DESIGN: Review of two randomized, controlled trials (RCTs) and one randomized, open-label, controlled pilot study published between 2014 and 2017. Each included study was published in a peer reviewed journal in English language.

DATA SOURCES: Two RCTs and one pilot study were researched via PubMed.

OUTCOMES MEASURED: Resolution of Clostridium difficile infection (CDI) was measured via written subject diaries of symptoms for adverse events, stool pattern and CDI episodes. Clinical resolution of diarrhea was measured via structural questionnaires and written subject diaries of discomfort, bowel movements and stool type using the Bristol Stool Chart, total number of bowel movements per 24-hour period, abdominal discomfort and intolerance to treatment, and weekly communication after the last fecal microbiota transplant.

RESULTS: The RCT by Lee, et al. showed a statistically significant resolution of diarrhea without relapse at 13 weeks and adverse events with frozen fecal microbiota transplantation (FMT) (P=0.01). The RCT by Jiang, et al. did not show a statistically significant resolution of CDI during the 5 months after transplant with frozen FMT versus fresh FMT (P=0.233). The pilot study by Youngster, et al. did not show a statistically significant clinical resolution of diarrhea without relapse after 8 weeks with nasogastric versus colonoscopic administration of frozen fecal microbiota (P=0.628).

CONCLUSION: The evidence to determine whether frozen FMT is as effective as fresh FMT administered via NGT versus colonoscopy in treating adults with CDI is conflicting. The RCT by Lee, et al. provided adequate evidence that frozen FMT is non-inferior to fresh FMT at inducing clinical resolution of diarrhea in CDI. However, the RCT by Jiang, et al. did not reach statistical significance, thus, further investigation is warranted to adequately determine the effectiveness of frozen FMT at treating CDI. The administration of frozen FMT via nasogastric tube also requires further investigation as Youngster, et al. demonstrated a lack of statistical significance compared to colonoscopic administration of frozen FMT.

KEY WORDS: Fecal microbiota transplant, Clostridium difficile

INTRODUCTION

Clostridium difficile infection (CDI) is one of the most common causes of nosocomial infectious colitis and is frequently associated with antibiotic therapy. Historically CDI has been more prevalent amongst the elderly, hospitalized and long-term care patient populations; however, the epidemiology is rapidly evolving and previously low risk populations such as the antibiotic-naïve and those without recent healthcare encounters are being impacted.[1] The severity of symptoms of CDI can range from mild abdominal discomfort, cramping and lose stools to hematochezia, continuous diarrhea and severe dehydration requiring hospitalization and prompt medicinal intervention. CDI is associated with significant and rising morbidity and mortality, as well as life-threatening complications including pseudomembranous colitis, bowel perforations, toxic megacolon and sepsis. CDI has become a growing medical concern as recurrence rates are on the rise with greater than 60% of patients experiencing relapse after initial infection, indicating that patients are failing conventional antibiotic therapy.[2]

Based on data from 2008 and 2009, there were 349,000 and 336,600 CDI-related hospital admissions in the US, respectively.[1] CDI-related admissions accounted for nearly 1% of total hospital admissions in 2009, and 92% of these admissions were patients $\geq$65 years of age.[1] In 2015 in the United States alone, the mean financial burden of a patient hospitalized due to CDI was $21,448 and the annual total cost attributable to CDI was 6.3 billion dollars.[3] The annual hospital management and inpatient treatment of CDI in 2015 amounted to approximately 2.4 million total days of inpatient stay.[3] The exploration of alternative treatment options is imperative to improving both the financial and healthcare associated burdens that have risen as CDI has evolved in terms of treatment resistance, recurrence and epidemiologic impact.

Clostridium difficile is an anaerobic, gram-positive bacillus that is the primary causative agent of pseudomembranous colitis and antibiotic-associated diarrhea known as CDI. Within the last 15 years, the US incidence of CDI has tripled.[4] Patients most likely to be hospitalized for CDI are females 85 years of age and older. While CDI was once viewed as a medically manageable complication of antimicrobial therapy, it has reemerged in the twenty-first century as a potentially refractory, severe infectious disease.[1] Usage of broad spectrum antibiotics such as ampicillin, clindamycin, fluoroquinolones and third generation cephalosporins are associated with a higher risk of CDI. A healthy gastrointestinal tract consists of a diverse microbial gut biome that serves as a defense mechanism against pathogenic microbes. Although antimicrobial therapy ideally wipes out pathogenic organisms, CDI can result as the ability of indigenous microbes to prevent the colonization of pathogenic organisms such as *C. difficile* may be impeded.

Ironically, the first line treatment for CDI is antibiotic administration aimed to prevent further growth of *C. difficile* and improve symptoms. Based on the recently updated IDSA/SHEA guidelines, oral vancomycin or fidaxomicin should be utilized as gold standard therapy for CDI regardless of severity.[6] In mild to moderate CDI when neither of these antibiotics are available or are contraindicated oral metronidazole may be used. Patients who experience recurrent or refractory CDI are often treated with prolonged oral vancomycin tapers. An alternative treatment to antibiotic therapy for recurrent CDI is FMT. While CDI alters the colonic microbiota, FMT can replenish the normal gut flora without prolonged antibiotic therapy and its subsequent side effects. Fresh and frozen fecal products obtained from qualified donors and administered by the upper and lower GI tracts are being explored as curative treatments for recurrent and refractory CDI. This paper utilizes two randomized controlled trials (RCTs) and

one randomized, controlled pilot study to evaluate the effectiveness of both frozen versus fresh fecal microbiota transplantation (FMT) and FMT delivered via nasogastric versus colonoscopic administration at treating CDI.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not "is frozen fecal microbiota transplantation as effective as fresh fecal microbiota transplantation via colonoscopic versus nasogastric tube administration in treating adults with Clostridium difficile infection?"

METHODS

The studies included in this review are two randomized, controlled trials and one randomized, open-label, controlled pilot study. The populations of interest were adults over the age of 18 years old with recurrent or refractory CDI. The interventions being evaluated were frozen FMT and frozen FMT administered via nasogastric tube (NGT) compared against fresh FMT and frozen FMT administered via colonoscopy. The outcomes measured in these studies were clinical resolution of diarrhea without relapse after 8 weeks, resolution of CDI, and clinical resolution of diarrhea without relapse at 13 weeks and adverse events. The key words utilized in the data source search were fecal microbiota transplant and clostridium difficile.

Each of the included articles were published in peer reviewed journals in English language. The articles were researched via PubMed and selected based on their ability to answer my proposed clinical question with results measured in terms of patient oriented outcomes (POEMs). Inclusion criteria required that the studies be randomized, controlled and published within the last 10 years. Studies were excluded if the majority of participants were under the age of 18 years old. The summary of statistics reported include both NNT and p-value.

Table 1 – Demographics of Included Studies

Study	Type	# of Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Youngster (2014) (4)	Randomized, open-label, controlled pilot study	20	58.6 $\pm$ 19.6	Refractory or recurrent CDI: relapse of CDI after $\geq$3 episodes mild-moderate CDI and failure of 6-8 week taper with vancomycin OR $\geq$2 episodes of severe CDI resulting in hospitalization and associated with significant morbidity	Anatomic CI to NGT or colonoscopy, delayed gastric emptying syndrome, recurrent aspirations, pregnancy, significantly compromised immunity, history of significant allergy to foods not excluded from donor diet	0	Frozen fecal microbiota transplantation administered via nasogastric tube (NGT)
Jiang (2017) (5)	RCT	73	33-88	History of $\geq$ 3 separate bouts of CDI in past 12 months in nonpregnant adults $\geq$ 18 years of age	Previous recipient of a fecal microbiota transplant	1	Frozen fecal microbiota transplantation
Lee (2016) (2)	RCT	232	72.2 $\pm$ 15.9	Pts 18 years or older with history of recurrent or refractory CDI	Neutropenia, peripheral WBC counts $\geq$ 30.0 x 10^9/L, or toxic megacolon	25	Frozen fecal microbiota transplantation

OUTCOMES MEASURED

Youngster, et al.[4] addressed clinical resolution of diarrhea without relapse after 8 weeks which was defined as less than 3 bowel movements per 24 hours. Patients were followed with structural questionnaires administered on days 1, 2, 3, 7, 14, and 21, and at 2 and 6 months after the procedure (primarily by phone). Questionnaires recorded stool frequency and consistency, general well-being on a standardized health score, rating of gastrointestinal symptoms,

medication use, and weight changes, and elicited possible adverse events by use of a modification of the Common Terminology Criteria for Adverse Events version 3.0 approved by the FDA and institutional review board. Jiang, et al.[5] measured resolution of CDI with cure defined as freedom from bouts of CDI during the 5 months after FMT. Patients kept written subject diaries of symptoms at regular intervals for 5 months after FMT for adverse events, stool pattern and CDI episodes. Lee, et al.[2] addressed clinical resolution of diarrhea without relapse at 13 weeks and adverse events by patient diaries that recorded discomfort, bowel movements and stool type using the Bristol Stool Chart. Patients were instructed to record the total number of bowel movements per 24-hour period, abdominal discomfort and intolerance to treatment between days 1 and 12. Weekly communication was maintained after the last FMT to evaluate any evidence of recurrence or adverse events.

RESULTS

Within 6 academic medical centers in Canada, Lee, et al.[2] assessed the eligibility of 263 patients who were 18 years or older with histories of refractory or recurrent CDI, excluding those who met exclusion criteria. Utilizing a computer-generated random number system 232 patients were then assigned to receive either fresh or frozen FMT delivered via enema (114 to receive frozen and 118 to receive fresh). Only 108 and 111 of the patients randomized to the frozen and fresh groups respectively received the enemas as randomized, which formed a modified intention to treat (mITT) population. The mITT population included all patients who were lost to follow-up, received one FMT but required antibiotic therapy afterwards, received both types of FMT or required antibiotic therapy for additional infections. The per-protocol population of 91 and 87 patients randomized to frozen and fresh groups respectively consisted of patients who received two FMTs of the same type, did not receive antibiotic therapy between enemas and did not

require antibiotic therapy for additional infections. For the evaluation purposes of this review the per-protocol population was utilized.

To ensure that the study remained double-blind the enemas were prepared by an unblinded laboratory technician. The patients received 50 mL of either fresh or frozen FMT via enema on day 1 and those whose CDI showed no signs of improvement by day 4 received a second enema between days 5 to 8. Patients nonresponsive to both FMT enemas were considered treatment failures and offered a third enema or antibiotic therapy. The primary clinical outcome addressed was clinical resolution of diarrhea without relapse at 13 weeks and adverse events. Within the per-protocol population, 76 of 91 (83.5%) in the frozen FMT and 74 of 87 (85.1%) in the fresh FMT fulfilled the primary outcome, demonstrating that frozen FMT was non-inferior to fresh FMT (95% CI -10.5-∞; P=0.01). RBI, ABI and NNT are calculated in Table 2. The most common adverse events (AEs) during the follow-up period were constipation (20%) and excessive flatulence (25%), without any difference in proportion of these events between the two groups. Serious adverse events (SAEs) were defined as a life-threatening event, death, new or prolonged hospitalization or newly developed significant impact on daily activities. At the 13-week follow-up, 29 SAEs occurred although none were found to be attributable to the FMT based on blinded investigation. In total 4 patients died from unresolved CDI, 2 in each the fresh and frozen groups. Refer to Table 3 for AEs and SAEs due to FMT.

Youngster, et al.[4] studied 20 patients aged 7-90 years old with refractory or recurrent CDI as defined by inclusion criteria who were recruited via referral from colleagues at Massachusetts General Hospital. A computer-generated randomization system was utilized to assign patients to treatment arms to evaluate the effectiveness of frozen FMT delivered via nasogastric versus colonoscopic administration; however, as an open-label study both the patients and investigators

were aware of the treatments being administered. The 10 patients allocated to colonoscopic frozen FMT group completed standard bowel preparation and received 90 cc thawed fecal product in the right colon, as well as one dose of Loperamide to promote product retention. Forty-eight hours prior to the procedure, the 10 patients in the NGT frozen FMT group were administered 2 mg/kg/day of omeprazole, and then received 90 cc of thawed fecal product via appropriately sized NGT. Patients who exhibited no signs of improvement in both arms were offered a second FMT via route of administration of their choice. All 20 patients received the treatments they were randomized to and no patients were lost to follow-up.

The primary clinical outcome addressed was clinical resolution of diarrhea without relapse within 8 weeks of follow-up. Follow-up for those who received a second FMT began the day of the second administration, thus, all clinical outcomes were measured according to the intention-to-treat analysis. All statistical tests were considered two sided with a P-value of <0.05 indicating statistical significance and categorical variables were compared using the Fisher exact test. After the first administration of FMT, 6 of 10 (60%) patients in the NGT group met the primary outcome, compared to 8 of 10 (80%) in the colonoscopy group (P=0.628). One patient in the original NGT group denied a second FMT, while the remaining 5 received frozen FMT via NGT. After the second FMT all four patients from the original colonoscopy group met the primary outcome, resulting in a 10 of 10 (100%) cure rate compared to 8 of 10 (80%) in the NGT group (P=0.53). RBI, ABI and NNT are calculated in Table 2. Of the two patients who failed treatment, one refused further FMT administration and the other was later discovered to have been self-administering homemade fecal enemas daily the week prior to the study. AEs associated with the FMT such as abdominal discomfort and bloating were experienced by 4 of 20

patients (20%). None of the SAEs that occurred were found to be related to the FMT by investigators (Table 3).

Jiang, et al.[5] assessed 73 patients 18 years of age or older who met inclusion criteria to evaluate the effectiveness of fresh versus frozen FMT delivered by colonoscopy at a single out-patient clinic in Houston, Texas. Randomization was utilized to assign 25 patients to both the fresh and frozen FMT groups, although one patient in the frozen microbiota group was lost to follow-up. To maintain double-blinding the laboratory director was the only individual aware of the product assignments. Each of the patients completed standard bowel preparation the night prior to receiving the allocated FMT via colonoscopy performed by two gastroenterologists. The fecal product was delivered half in the proximal colon with the remainder infused progressively throughout the colon to the rectum.

The primary outcome measured was resolution of CDI. Although cure was defined as freedom from bouts of CDI at 5 months, the initial follow-up was completed after 2 months. At the two-month follow-up, 20 of 24 (83%) who received frozen FMT obtained resolution, compared to 25 of 25 (100%) in the fresh FMT group (CI 1.37-405.42; P=0.233). RBI, ABI and NNT are calculated in Table 2. According to the study there were no SAEs and the proportion of AEs between the two groups was equal. Within the first 2 days following FMT the most common AEs were nausea, mild diarrhea and abdominal discomfort (86%). It should be noted that the breakdown of AEs amongst the treatment arms included the use of lyophilized FMT that was not utilized for the purposes of this review and the percentage of AEs is skewed to include this population of patients (Table 3).

Table 2 – Calculations for Treatment from Lee, et al.[2], Youngster, et al.[4], and Jiang, et al.[5]

Study	CER	EER	RBI	ABI	NNT	P-value
Lee, et al.	0.851	0.835	-0.019	-0.016	-63	0.01
Youngster, et al.	0.80	0.60	-0.25	-0.20	-5	0.628
Jiang, et al.	1.00	0.83	-0.17	-0.17	-6	0.233

Table 3 – AEs/SAEs related to FMT from Lee, et al.[2], Youngster, et al.[4], and Jiang, et al.[5]

Study	Adverse Events (AEs)	Serious Adverse Events (SAEs)
Lee, et al.	Fresh/Frozen: Constipation (20%) Excessive Flatulence (25%)	Frozen FMT: 2% Fresh FMT: 2%
Youngster, et al.	Fresh/Frozen: Abdominal Discomfort, Bloating (20%)	None
Jiang, et al.	NGT/Colonoscopy: Nausea, Abdominal Discomfort, Mild Diarrhea (86%)	None

DISCUSSION

Lee, et al.[2] demonstrated statistical significance supporting that frozen enema FMT is non-inferior to fresh enema FMT at inducing clinical resolution of diarrhea within 13 weeks in patients suffering from refractory or recurrent CDI. However, Jiang, et al.[5] did not exhibit statistical significance indicating that frozen FMT was not as effective at curing CDI as fresh FMT delivered via colonoscopy. The varying routes of administration of the FMT products in these studies cannot be ignored as a factor that could have impacted the effectiveness of the FMT and makes direct comparison of the outcomes less applicable. Although the results of Youngster, et al.[4] did not support that NGT administration of frozen FMT was as effective as colonoscopy based on lack of statistical significance, the study did indicate that clinical resolution of diarrhea without relapse after 8 weeks was more likely to be achieved with additional FMTs. While the mean age of patients in this study was 54 years old, all three pediatric patients that were included

received clinical cure after one administration of FMT, emphasizing the need for further investigation into the effectiveness of FMT in pediatric patients with CDI.

Numerous contraindications to FMT exist and must be evaluated to ensure patient safety and the prevention of undesired clinical outcomes. Patients in whom FMT is contraindicated are those who are pregnant, diagnosed with toxic megacolon or have anatomic abnormalities that could impact the delivery method. [7] In patients who cannot tolerate the anesthesia or bowel preparation required for colonoscopic administration NGT could be a viable option, which emphasizes the importance of further studies to determine its effectiveness. Each of these modes of delivery has associated risks that must also be weighed, such as aspiration with NGT and bowel perforation with colonoscopy.

Insurance coverage of FMT as a treatment for recurrent or refractory CDI is dependent upon the patient's ability to satisfy specific coverage criteria. If these criteria are met, most insurance companies offer coverage pending that the FMT is deemed medically necessary and not performed for experimental purposes. These criteria prolong the infectious process of CDI as patients must experience numerous recurrences or increased severity of episodes before coverage becomes available. The term 'coverage' also becomes ambiguous as insurance companies are not required to include the testing of donor stool, a medically necessary step to ensure that the fecal product is safe prior to administration.[8] Due to the risk of transmission of numerous infectious diseases including HIV, donor screening and stool sample testing are imperative to ensure the efficacy and safety of this treatment modality.

A major limitation to this search was the lack of RCTs utilizing the same interventions and comparisons in regard to FMT as a treatment for CDI. This made direct comparison of the results amongst these studies less reliable, as numerous confounding variables, primarily routes

of administration, exist amongst them. A limitation to the studies completed by Lee, et al. and Jiang, et al. was the limited follow-up at 13 and 8 weeks respectively, which are both insufficient time frames to properly evaluate the long-term efficacy and safety of FMT. To address the unknown long-term safety Lee, et al. is performing a 10-year follow-up on the patients in the study to evaluate the long-term positive and negative outcomes. The use of enemas to deliver FMT was another limitation of Lee, et al. as the effectiveness of enemas compared to other delivery methods must be evaluated in further studies. The notably small sample sizes in the trials performed by Youngster, et al. and Jiang, et al. also served as limitations.

CONCLUSION

The evidence to determine whether frozen FMT is as effective as fresh FMT administered via NGT versus colonoscopy in treating adults with CDI is conflicting. While Lee, et al. concluded that frozen FMT was non-inferior to fresh FMT, Jiang, et al. did not determine statistical significance between the two. Thus, additional studies are warranted to effectively evaluate both types of fecal products administered by the same route to determine which is superior in the utilization of FMT as a treatment for CDI. The effects of stool donors on FMT must also be further explored, as the donor selections within these three studies varied and introduced another area for future research. While NGT administration was not deemed statistically significant, its overall effectiveness was enforced by the 100% cure rate achieved in the colonoscopy group after a second NGT FMT administration. Studies with significant prolonged follow-up are necessary to determine the long-term outcomes associated with FMT. With the information provided by future studies a standard of care will be established to govern FMT and help to propel the most effective form of this treatment modality to the forefront in patients suffering from recurrent and refractory CDI.

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