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Original Article

The Preliminary Investigation of Faecal Microbiota Transplantation for Paediatric Recurrent Chronic Bowel Diseases and Literature Review

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Abstract ***Background:*** Faecal microbiota transplantation (FMT) is a potential therapeutic method to treat intestinal diseases with faecal dysbiosis. FMT has demonstrated effectiveness for recurrent *Clostridium difficile* infection (CDI), meanwhile it also showed potential therapeutic effect for some inflammatory bowel disease (IBD) patients. ***Methods:*** There were five patients, from 1Y6M to 11 years old. Two patients were diagnosed very early onset Crohn's disease (CD), two patients were ulcerative colitis (UC) and one patient was pseudomembranous colitis. They underwent FMT therapy by nasal jejunal tube or colonoscopy, and were followed up every two to four weeks after FMT. ***Results:*** One UC patient and the pseudomembranous colitis patient achieved partial remission after FMT. However, both of the patients' symptoms relapsed six to eight weeks after FMT. Two CD patients and one UC patient did not respond to FMT therapy. All of the IBD patients had moderate to severe disease active index before FMT. For adverse effects: four of the patients had fever after FMT. Other adverse events included abdominal pain, abdominal uncomfortable, they were mild and self-limiting. ***Conclusions:*** FMT had limited effect for very early onset CD and UC patients in our preliminary clinical experience. The incidence of adverse effects of FMT was much higher than reported.

Key words Crohn's disease; Faecal microbiota transplantation; Paediatrics; Pseudomembranous colitis; Ulcerative colitis

Introduction

Faecal microbiota transplantation (FMT) was referred to infuse faecal suspension from a healthy donor into the gastrointestinal (GI) tract of a patient through upper or lower way. FMT with a goal to rebuilt microbial community in the gut has become a research hotspot in recent years and was investigated as a new treatment method for a number of GI and non-GI disorders. FMT is effective in the treatment of *Clostridium difficile* toxin-induced recurrent colitis and has been recommend as the first line therapy for the recurrent and refractory *C. difficile* infection (CDI). FMT also showed therapeutic effect for other GI disorders and non-GI disorders such as inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), autoimmune diseases, and metabolic syndromes.

Although the efficiency of FMT for CDI is well admitted, the effect of FMT for other GI diseases is still obscure and without quality research. IBD including Crohn's disease (CD) and ulcerative disease (UC) are both chronic bowel disease, which have a bunch of data support the hypothesis that they result from the immune responses to the intestinal microbiota in genetically susceptible individuals. And such immune responses lead to dysbiosis which induce the inflammatory response. The detailed mechanisms of intestinal dysbiosis involved in the development of IBD are

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still not well elucidated. Decreased bacterial diversity and changes in the abundance of certain bacterial groups have been observed in the faecal samples and colonic biopsies of IBD patients, in comparison with the samples of healthy subjects, monozygotic twins, and multi-centre studies.[1-4] Several bacterial groups have been associated with IBD, including *Escherichia* and *Bacteroides spp.* as well as bacteria belonging to the *Clostridiales*. *Faecalibacterium prausnitzii*, an abundant intestinal bacterium belonging to the *Clostridium* cluster IV, was found to be frequently reduced in abundance in CD patients, and there was a reduction in the mucus-degrader Akkermansia muciniphila which has been reported in CD and UC patients.[3,5-7] It is suggested that feces contain a superior combination of intestinal bacterial strains and are more favourable for repairing disrupted native microbiota by introducing a complete, stable community of intestinal microorganisms. Feces also harbour additional substances (proteins, bile acids, and vitamins) which may contribute to the recovery of gut function.[8] Preliminary case reports of FMT for treating IBD patients revealed a mixed results for the patients were with different age, different disease activity, and different way of administer FMT. The condition of the FMT donator would also affect the treatment result.

Since the effect of FMT on intestinal disease is still exploring the way. This clinical research is a prospective study mainly to confirm the preliminary safety and potential efficacy of FMT in paediatric recurrent chronic bowel diseases including CD, UC and pseudomembranous colitis which failed to respond to regular medical treatment. However, FMT had limited effect for very early onset CD and UC patients in our preliminary clinical experience.

Methods

This was a single-centre open-label study designed to determine tolerability, preliminary safety, and potential efficacy in paediatric patients with chronic recurrent intestinal bowel diseases who did not respond to regular medical treatment. Each participant was followed in the study for more than 12 weeks. Patients were recruited from a tertiary hospital during July 2014 to July 2015. All patients provided written informed consent or assent. This research was also under the ethics of the hospital.

All patients had a diagnosis made by more than two experienced senior gastroenterologist based on history, physical examination, laboratory/radiological studies and gastrointestinal histology. Patients had laboratory tests, including complete blood count (CBC) with differential and platelets, C-reactive protein (CRP), albumin, stool studies for *C. difficile*, bacterial culture, ova and parasite. Donor History Questionnaire was used to evaluate study participant donors for ruling out gastric and intestinal disease, surgery of gastric and intestinal, infectious disease, diabetes, metabolic syndromes, autoimmune disease, allergic disease such as asthma, eosinophilic gastroenteritis. Faecal donor laboratory studies included hepatitis A antibody, hepatitis B serum antigen, hepatitis C antibody, human immunodeficiency virus antibody, rapid plasma reagin and Epstein-Barr viral IgG and IgM, cytomegalovirus IgG and IgM, as well as stool testing for *C. difficile*, bacterial culture, and examination of stool for ova and parasites. The donor for each patient was one of their parents. Donors should also prevent to take antibiotics in three months before the FMT procedure.

Patients received vancomycin 15 mg/kg three times daily for three days until the evening before the procedure. Patients also received omeprazole (0.7 mg/kg intravenous) on the day before and morning of the procedure if via upper gastric way. Transplant recipients received phenolphthalein tablets (<6 years old) or Bisacody (>6 years old) for four days as the same bowel preparation as colonoscopy. For upper gastric way, a nasojejunal (NJ) feeding tube was placed for transplant in the morning of transplantation. Location of the tube was confirmed by X-ray. For lower gastric way, faecal was transplant through colonoscopy or by enema. Approximately 30 g of donor stool was mixed with 100 mL to 200 mL of normal saline and blended with a home used blender at low speed for two to four minutes until a homogenous texture was obtained. The homogenous stool was then filtered two to four times using gauze. Prepared stool was used within half an hour. Infusion was slowly administered through NJ tube over half an hour or through colonoscopy over five to ten minutes period. The NJ tube was flushed with 15 mL of normal saline over 10 minutes. The NJ tube was removed after 15 minutes.

FMT recipients stayed in hospital for at least three days after transplantation and had clinical follow-up at two, four, eight and 12 weeks. CBC, CRP and erythrocyte sedimentation rate were checked when followed up. Clinical manifestations, physical examinations and any possible side effects reported by patients and their parents were recorded.

Results

There were five patients received FMT, including four male patients and one female patient. The age of patients were ranged from 1Y6M to 11 years old, among them two patients were under three years old. Case 1 was diagnosed pseudomembranous colitis. Case 2 and case 3 were diagnosed very early onset CD, while the paediatric Crohn's disease active index (PCDAI) sore were 37.5 and 75 respectively before FMT. Case 4 and case 5 were ulcerative colitis, meanwhile the paediatric ulcerative colitis disease active index were 30 and 57.5 respectively before FMT. The duration of disease was from one month to four years, and three of them were longer than one year. The lesion of disease mainly involved colon according to colonoscopy and magnetic resonance enteroclysis, however the disease lesion of case 2 was involved small intestinal bowel as well. All the donors were their mother living together with them except the donor of case 5 was her father.

The general condition and medicines these patients taken before FMT were listed in Table 1. Case 1 and case 4 achieved partial remission after FMT, however the symptoms relapsed around six to eight weeks after FMT. Case 2, case 3 and case 5 did not respond to FMT. Furthermore, the condition of patients got worse with case 5. Case 1 showed response immediately after FMT. He had formed stool without blood the second day after FMT. The colonoscopy also showed great improvement of colon inflammation one month later. However the symptoms relapsed around six weeks after FMT, with a bit fresh blood in the stools. He still had a bit fresh blood at the end of bowel movement after another FMT. Case 4 had fewer times of bloody stools and the stools were of shapes after FMT. He was steroid dependent before, however the dose of steroid was reduced to half of original dosage after FMT. The colonoscopy showed that this patient was improved one month later as well. The inflammation markers were gradually reduced to normal level later. However, his symptoms relapsed around eight weeks after FMT. He still had several episodes of bloody stool after the second FMT. Case 2, case 3 and case 5 had persistent fever with obviously elevated inflammatory markers after FMT, and their symptoms did not get any improvement, case 5 got worse after FMT. Her diarrhoea was deteriorated with fresh and dark blood in the stools.

Adverse effects (Table 2): One patient reported he had mild abdominal uncomfortable, while two patients had mild abdominal pain after colonoscopy. Four patients had fever after FMT. Case 4 had mild fever after the first time of FMT, accompanied with slight elevation of inflammatory makers. Another three patients had persistent fever after FMT accompanied with obviously elevated inflammation markers. All of the three patients considered to have infection although the stool and blood culture were negative. They both received antibiotic treatment intravenously. Additionally, the NJ tube insertion was really an uncomfortable experience for children. The bowel preparation and the colonoscopy for the FMT also bring uncomfortable experience to the children.

Table 1 General information for patients

Patients	Gender	Age	Diagnosis	Disease duration	Symptoms	Treatment
1	M	11 years	Pseudomembranous colitis	2 years	Bloody stools	Vancomycine, metronidazole
2	M	2-year-1-month	Crohn's disease	2 years	Fever, perianal abscess, diarrhoea	Antibiotics, prednisone, mesalazine
3	M	1-year-6-month	Crohn's disease	1 month	Fever, diarrhoea, perianal abscess	Antibiotics, TPN
4	M	7 years	Ulcerative colitis	4 years	Bloody stools	Prednisone, mesalazine, methotrexate
5	F	10-year-9-month	Ulcerative colitis	4 years	Bloody stools	Prednisone, mesalazine, PN+EN

TPN: total parenteral nutrition, PN: parenteral nutrition; EN: enteral nutrition

Discussion

FMT was an old method which had applied in the modern medicine to treat intestinal and non-intestinal diseases. FMT was well accepted applied to treat CDI. The published experience of FMT for IBD showed potential treatment effect. The first UC patient received FMT therapy was in 1989, after he was transferred by enema, his clinical symptoms and pathological manifestation of intestinal mucosa were all got remission without using any medicine for 11 years.[9] Borody reported six severe UC patients after FMT the symptoms and histological appearance of intestinal mucosa all got improvement in 2002. He analysed 62 UC patients with the treatment of FMT, and found that over 90% of patients got clinical improvement, 67.7% of the patients had complete remission. 24.2% of the patients had partial remission. There were only 8% percent of patients failed to response.[10] Patrizia k reported six chronic active UC patients received FMT through colonoscopy. Both of the six patients' symptoms got improved in two weeks, but only one of them got clinical remission. And the microbiota analysis revealed three of them the microbiota were resemble to the donators.[11] There was UC patient with anal fistula, the regular therapy did not work. After he received FMT therapy four weeks later, the clinical symptoms, endoscopic appearance and pathological manifestation all got remission.[12] However, there were few studies of paediatric study since FMT had applied. David reported four UC children received FMT therapy through NG tube in 2014. These patients were followed 2 weeks, 4 weeks and 12 weeks after FMT. None of them got clinical remission.[13] In 2014, a meta-analysis revealed 111 IBD patients had received FMT therapy. Among these patients, 77.8% of the IBD patients had clinical improved. Nearly 90% UC patients had clinical improved including the clinical symptoms and reduce of UCAI score. Only three studies refer to children. The results of paediatric group varies, but none of them had sever adverse effect. With diagnose of CDI, all the patients including children all got excellent results. It indicated these patients' clinical improvement mostly owning to the improvement of CDI but not UC.[14] As to CD patients, most of the studies did not achieve exciting results except several case reports had inspiring result. David L also reported nine CD patients from 12 to 19 years old with mild to moderate symptoms according to PCDAI received FMT by NG tube and followed up at two, six, 12 weeks after FMT. Based on PCDAI, seven of nine patients were in remission at two weeks and five of nine patients who did not receive additional medical therapy were in remission at six and 12 weeks. Metagenomic evaluation of stool microbiome indicated the evidence of FMT engraftment in seven of nine patients.[15]

In our preliminary clinical study, all the five patients presented chronic recurrent bowel disease. Their symptoms were refractory or persistent after regular medical therapy. The clinical and endoscopic results showed two patients were improved after the FMT therapy. Three patients did not respond to FMT, meanwhile they had persistent fever caused by secondary infection. Case 1 was a pseudomembranous colitis patient, *clostridium difficile* test was negative. The therapeutic effect of FMT was as good as reported, however the symptoms relapsed around six weeks. Case 2 and case 3 were both very early onset CD patients and their PCDAI sores reveled moderate to severe disease activity. Both of them had persistent fever with elevated inflammatory makers after FMT, which were considered as secondary infection caused by FMT. One of the UC patients had partial remission after the first FMT, and the symptoms relapsed around eight weeks. Another UC patient failed to respond to FMT therapy. In our study, FMT did not showed positive therapeutic effect for both very early onset CD and UC patients. The most common reported adverse effects were mild to moderate abdominal pain or distension, and they usually were self-limiting. FMT was reported safe for severe case of CD patient even with sepsis patient. In our

Table 2 Adverse effects of patients and treatment

Patient	Adverse effects	Treatment
1	Abdominal distension	Self- limited
2	Persistent fever, elevation of WBC and CRP, infection	Antibiotic and steroid
3	Persistent fever, elevation of WBC and CRP, infection	Antibiotic
4	Transient fever, transient elevation of CRP, abdominal pain	Self-limited
5	Persistent fever and elevation of WBC and CRP, abdominal pain	Antibiotic and intravenous immunoglobulin

WBC: white blood cells; CRP: C-reactive protein

study, although the stool donators were all exclude infection by stool and blood test before FMT and the patients' stool and blood cultures were all negative, the rate of infection caused by FMT in our study was much higher than reported. It was considered that the high risk of infection rate might had relationship with the high disease activity index and young age. Therefore, we should be more cautious with patients with high disease activity index when apply FMT, which may cause secondary infection. It was a pity that the microbiome of the patients had not been analysed to make sure whether the faecal microbitota from donor was colonised after the FMT in this study. Thus we did not know the colonisation of microbiota from donor was correlated to the effect of FMT.

The pathogenesis of IBD is far more complex than CDI. Although it is related to the microbiota and immune of the intestine, the exact mechanism of IBD pathogenesis has not been clarified yet. The faecal microbiome composition of IBD patients has shown to be different from healthy individuals. A decreased bacterial load and variety are shown in IBD patients. The exact composition of the stool transferred by FMT, the benefit species of bacteria, immune material, and nutrition are not clarified. Moreover, the composition of the microbiota is affected by the species, sex and diet. The efficiency of FTM is affected by a variety of issues. More studies are needed to further verify whether FMT is beneficial for paediatric IBD patients, and how to choose the appropriate receptor and appropriate donor for FMT.

In conclusion, it was suggested that FMT should be more cautious with young age and high disease activity index patients in our preliminary study. And the effect of FMT is limited for paediatric IBD patients as so far.

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Conflicts of Interest Statement

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