Faecal microbiota transplantation for patients with irritable bowel syndrome: abridged secondary publication

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KEY MESSAGES

1. Faecal microbiota transplantation, delivered twice at an interval of 4 weeks, was not associated with overall improvement in irritable bowel syndrome symptoms.
2. Faecal microbiota transplantation relieved the most annoying symptom—abdominal bloating—likely by reducing hydrogen sulphide–producing bacteria in the gut.
3. Additional studies are needed to determine the optimal regimen.

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Introduction

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder worldwide. Observational studies have shown that faecal microbiota transplantation (FMT) delivered via the upper or lower gastrointestinal tract improves IBS symptoms, but randomised trials have yielded conflicting results.[1] An observational study revealed that seven of 10 patients with IBS achieved significant clinical improvement after a second dose of FMT,[2] suggesting that a second dose of FMT can enhance the therapeutic response.

The composition of faecal microbes in patients with IBS may affect the therapeutic efficacy of FMT. Some studies have identified certain bacteria and their metabolites, such as *Bacteroides* and butyric acid, as key determinants of the treatment response after FMT.[3] However, most published microbiota profiles have been based on the 16S RNA sequencing. The mechanism by which FMT relieves specific symptoms of IBS is unknown.

We hypothesised that FMT could relieve specific IBS symptoms by modulating the gut microbiota. We assessed the efficacy of FMT, delivered twice at an interval of 4 weeks, in relieving symptoms of IBS. We also explored associations between changes in gut microbiota signatures and clinical symptoms.

Methods

In this randomised, double-blind, placebo-controlled study, patients with IBS meeting the Rome III criteria were randomly assigned (in a 1:1 ratio) to receive frozen FMT from healthy donors or placebo via the duodenal route at baseline and week 4. Patients were assessed at baseline, week 4, week 8, and week 12 using a questionnaire. The primary outcome was clinical response, defined as a decrease of ≥75 points in the IBS severity scoring system (IBS-SSS). Secondary outcomes were improvement in general symptoms and improvement in bloating at week 12. After the trial, open-label FMT was provided for patients who had received placebo.

Stool samples were collected at baseline, week 4, week 8, and week 12 for DNA extraction. Extracted DNA was used to construct DNA libraries. Raw sequence data were quality-filtered to remove adaptors, low-quality sequences (quality score <20), and reads shorter than 50 base pairs. Contaminating reads were filtered with default parameters. Microbiota profiles were inferred from quality-filtered forward reads; species with average abundance <0.15% and prevalence <5% were filtered out. Microbiota functional annotation was then profiled.

Continuous data were compared using the Mann-Whitney *U* test, and categorical variables were compared using the Chi-squared test or Fisher's exact test (expected count <5). Within-group differences in IBS-SSS score over time were compared using repeated measures analysis of variance. Associations of specific microbial species with clinical parameters were identified using the multivariable analysis by linear models.

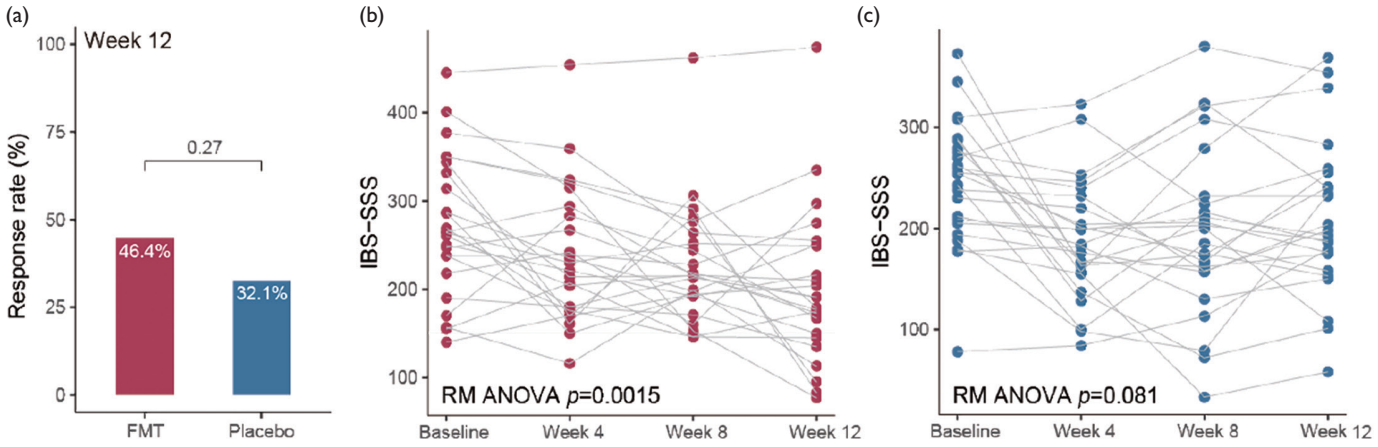

FIG 1. (a) Clinical response at week 12 and irritable bowel syndrome severity scoring system (IBS-SSS) scores over 12 weeks in (b) faecal microbiota transplantation (FMT) and (c) placebo arms

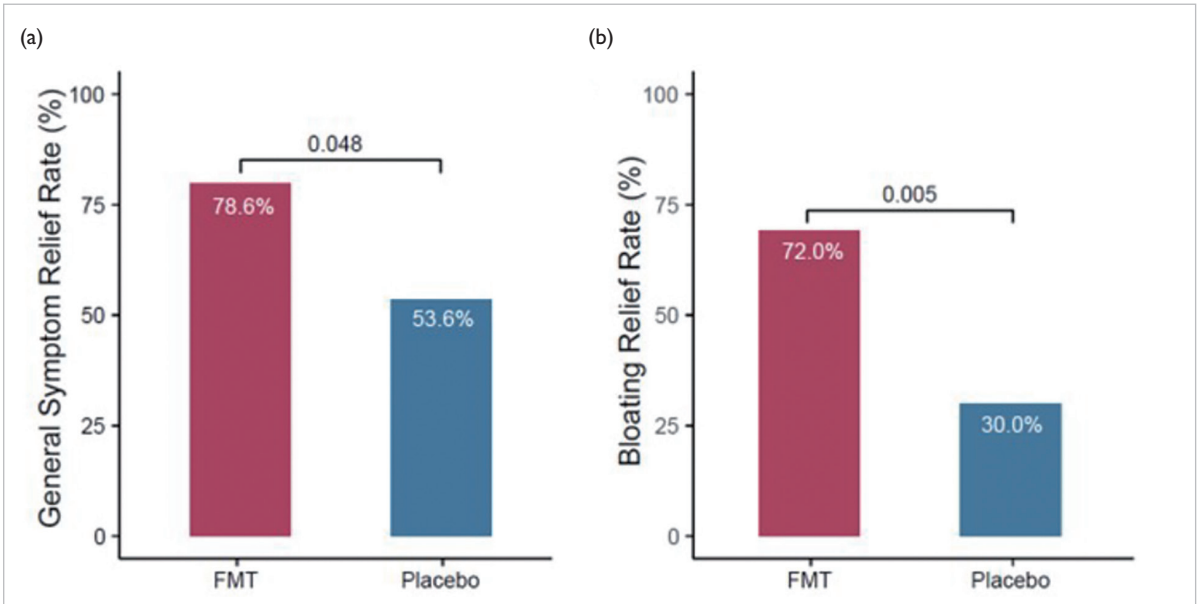

FIG 2. Self-reported (a) general symptom and (b) bloating relief rates at week 12 in faecal microbiota transplantation (FMT) and placebo arms

Results

Between April 2017 and September 2021, 56 patients with diarrhoea-dominant IBS were randomly assigned to receive FMT (n=28) or placebo (n=28). At week 12, 13 (46.4%) patients in the FMT arm and nine (32.1%) patients in the placebo arm had clinical response (P=0.27, Fig 1). Patients in the FMT arm showed a significant reduction in IBS-SSS score (P=0.0015), whereas no significant change was observed in the placebo arm (P=0.081). Higher proportion of patients in the FMT arm had improvements in self-reported general symptoms of IBS (78.6% vs 53.6%, P=0.048) and abdominal bloating (72% vs 30%, P=0.005) [Fig 2]. The two arms were comparable in terms of stool consistency, abdominal pain, IBS-quality of life score, or Generalised Anxiety Disorder-7 score. Clinical response was achieved in seven (30.4%) of 23 patients in the FMT arm, with improvements in IBS-SSS score (P=0.00067), IBS-quality of life score

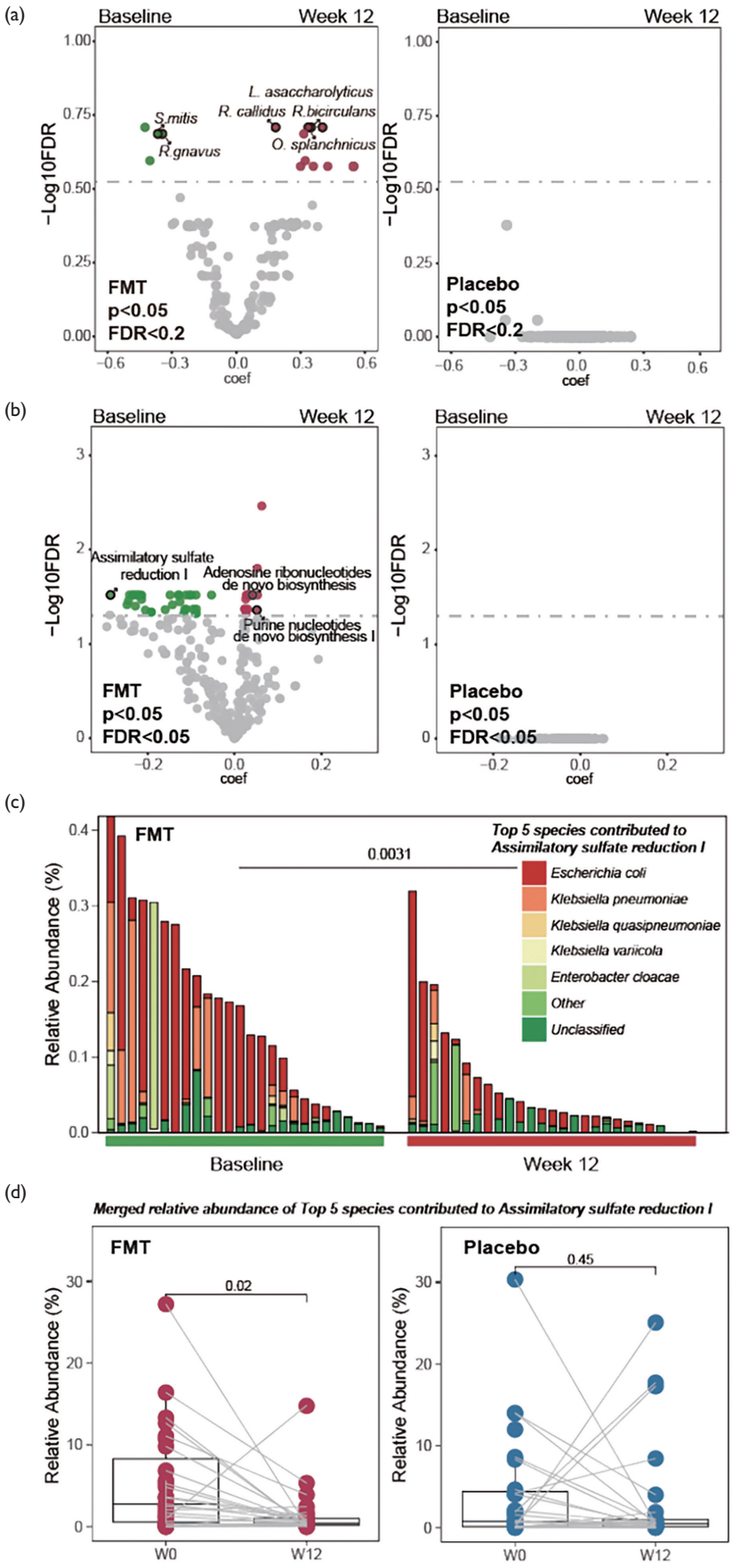

FIG 3. Faecal microbiota (a) composition at species level and (b) functional dynamics from baseline to week 12 in faecal microbiota transplantation (FMT) and placebo arms. False discovery rate (FDR) of <0.2 was considered statistically significant. (c) Contributions and (d) merged relative abundance of top five bacterial species to the assimilatory sulphate reduction I pathway.

(P=0.03), Generalised Anxiety Disorder-7 score (P=0.011), and abdominal pain (P=0.026), compared with baseline. Additionally, general symptom relief and bloating relief were achieved by 73.9% and 82.4%, respectively, of patients receiving open-label FMT at week 12.

Faecal microbial diversity (Shannon) and richness (observed number of species) did not significantly change from baseline to week 12 in the FMT or placebo arm (P>0.05). At week 12, the gut microbiota profile among patients in the FMT arm did not significantly shift toward the profile of the donors (P>0.05) but showed a significantly greater dissimilarity relative to baseline, compared with patients in the placebo arm (assessed by Bray-Curtis dissimilarity, P=0.03). Importantly, among patients who received FMT, the abundances of several potential beneficial bacteria (eg, *Lawsonibacter asaccharolyticus*, *Ruminococcus bicirculans*, *Odoribacter splanchnicus*, and *Ruminococcus callidus*) were significantly increased, whereas the abundances of several pro-inflammatory bacteria (eg, *Ruminococcus gnavus* and *Streptococcus mitis*) were significantly decreased (P<0.05, false discovery rate <0.2, Fig 3). However, no significant change at the species level was observed in the placebo arm at week 12, compared with baseline. In the FMT arm, the relative abundances of 22 metabolic pathways were significantly increased and those of 34 pathways were significantly decreased at week 12, compared with baseline (false discovery rate <0.05). The metabolic pathway with the greatest reduction in patients who received FMT was assimilatory sulphate reduction I, which produces hydrogen sulphide and may contribute to bloating. The top bacterial species that contribute to the assimilatory sulphate reduction I pathway were identified as *Escherichia coli* and several *Klebsiella* spp (Fig 3). There was a significant decrease in the total relative abundance of these bacteria in the FMT arm (P=0.02), but no significant change was evident in the placebo arm.

Discussion

Although FMT received twice at an interval of 4 weeks did not result in significant improvement in global IBS symptoms as measured by the IBS-SSS score, it improved abdominal bloating by >2-fold and self-reported general symptoms by 1.5-fold at week 12. This sustained improvement could be explained by the changes in the gut microbiota; FMT led to inhibition of gas-producing bacterial pathways and reduced abundances of hydrogen sulphide–producing bacteria in the gut. Our metagenomic analysis of bacterial functional pathways may provide a plausible biological explanation for this. Patients with IBS have higher faecal abundances of *E coli* and several *Klebsiella* spp, compared with non-IBS controls.[4] These putative pathogens may contribute to intestinal production of hydrogen sulphide, which can cause diarrhoea and bloating. Hydrogen sulphide is also a potential biomarker for small intestinal bacterial overgrowth in diarrhoea-predominant IBS.[5] Our results showed that FMT significantly decreased hydrogen sulphide production by reducing the abundances of *E coli* and several *Klebsiella* spp, which may partly explain significant relief from abdominal bloating. We speculate that FMT can be beneficial for a specific subgroup of patients with IBS whose predominant symptom is abdominal bloating.

This study had some limitations. First, it was not designed to target patients with IBS who report bloating. A larger sample size involving more homogenous patients with IBS who report bloating is needed to confirm our findings. Second, we speculate that the bloating improvement was related to the reduced abundances of hydrogen sulphide–producing bacteria. Animal experiments are required to confirm this mechanism. Third, analyses according to IBS subtype were not performed because of the limited sample size. Fourth, the sample size and number of donors were not sufficient to assess the donor effect on the efficacy of FMT for treating IBS. Optimisation of donor-recipient pairing may further improve the clinical response rate. Further research is needed to determine the optimal selection criteria for FMT candidates and optimal microbiota profiles of donors. Fifth, symptoms of abdominal distension or bloating were self-reported by patients; objective assessments, such as breath tests, would provide more insights. Sixth, we did not compare FMT with other treatment options (eg, training in abdominal relaxation techniques). Further research involving additional objective assessments and comparisons with other treatment options is needed to guide clinical applications of FMT in IBS treatment.

Conclusions

In patients with IBS whose predominant symptom is abdominal bloating, FMT is a safe, feasible, and effective treatment, probably owing to reduced abundances of hydrogen sulphide–producing bacteria in the gut. Our findings may help policymakers, health service managers, and service providers develop guidelines and implement FMT services in hospitals. Future studies should focus on patient selection, dosing regimens, and cost-effectiveness.

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Disclosure

The results of this research have been previously published in:

1. Yau YK, Su Q, Xu Z, et al. Randomised clinical trial: faecal microbiota transplantation for irritable bowel syndrome with diarrhoea. Aliment Pharmacol Ther 2023;58:795-804.
2. Su Q, Yau YK, Ng SC. Editorial: Faecal microbiota transplantation in IBS-Moving closer or away from success? Authors' reply. Aliment Pharmacol Ther 2023;58:952-3.

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