

Answering Reviewers

Dear Editor

We appreciate very much the reviewer's comments and constructive criticisms. We thank the reviewer for the time and effort spent on reviewing the manuscript and for their deep comments on the manuscripts.

Reviewer 1

1. "Title: Maybe include something like "Responses to faecal microbiota transplantation is similar between female and male patients with irritable bowel syndrome"

Response: Following the advice of reviewer 2 to perform subgroup analysis, we found a higher response rates and lower total IBS-SSS score in female patients with IBS-D. The suggested change in the title would not describe the findings of the study. However, we changed the title to indicate that it is a randomised, double-blind, placebo-controlled study.

2. "Introduction: -I would use a more recent manuscript for the sex ratio. -"

Response: This was done.

3. and 4. Methods: I think you should control the main results for age while the age between male and female are different in the placebo and treatment group, but also for subtypes while FMT is probably more efficient in the IBS-D subgroup!

Results: -Why the number of males in the placebo group is so small? Why haven't you randomized between FMT and placebo with the same sex ratio in your previous study? -Table 1: add the % for IBS subtype; and the p value for each line between the female and male in each group! -How do you explain a better quality of life in the male of the placebo group? -Even if the IBS-SSS was not different between the group (but what are the p value?) the distribution seemed to be different. You should discuss it. -Are your results normally distributed even in the male of the placebo group? if not you should present the results as median [Q1;Q3].

Response: this was done in table 1 (marked yellow) The results were normally distributed.

5. Discussion: -"Furthermore, the total scores on the IBS-SSS, FAS and IBS-QoL did not differ between females and males in both the placebo and the active treated groups before FMT and at different times after FMT" it is not true for IBSQOL at baseline in the placebo group neither for fatigue at 3 months in the placebo group!

Response: This was corrected in page 9, lines 1 from the bottom and page 10, lines 1-5 (marked yellow).

6. -page 10 "At 1 year after FMT levels of isobutyric and isovaleric acids were Increased in IBS patients, indicating a shift in microbial fermentation from a saccharolytic to a proteolytic pattern" Correct Increased for increased -the discussion should be more detailed!

Response: This was done in page 10, line 9 and lines 5- from the bottom (marked yellow).

Reviewer 2

Major comments:

1. The authors discussed the possible reasons for different results in study by Holvoet et al.

- i) One of the reasons suggested by the authors is different patient subgroups enrolled in the two studies. Therefore, it raises the question of what are the treatment responses between the two genders in each subgroups enrolled in this study? Are there any differences?

Response: This was done and the results were added in page 8, lines 4-8 and lines 10-16 from the bottom and 4 tables were added Tables 2, 3, 5 and 6. The findings were added to the abstract page 2 lines, 1-3 from the bottom and page 3 lines, 1-2, and lines 5-6. The findings were also added to the core tip page 3, lines 1-3 from the bottom and discussed in page 11, lines 5-9 from bottom, page 12 lines 1-2 and page 11 lines 4-8 (all marked yellow)

Thanks to the reviewer that an explanation to the discrepancy between our results and that of Holvoet *et al* could be reached. Without her/his comments and the subgroup analysis, this would be missed

- ii) The dose of the faeces used for FMT is another possible reason that caused the different results. In the current study, the authors allocated patients to receive either 30 or 60g faeces. Do they observe different responses with different FMT doses?

Response: this was done in page 11, lines 10-12 from the bottom (marked yellow)

2. Table1. The demographic data need more clarifications.

- i) What is the “Median” of the age in each groups
- ii) The age of disease onset
- iii) In the active treated group, are there any statistic differences in male vs female patient numbers/percentage with severe and moderate symptoms?
- iv) Overall, are these demographic features between (sub-) groups statistically different?

Response: All these changes were done in Table 1 (marked yellow).

“3. Table 2-4 & Table 7.

- i) Overall, graphic presentation of the data, as in bar graphs or individual time-line charts before and after treatment, should be added in addition to table.

- ii) Patients of moderate and severe symptoms should be separately plotted and statistically compared.
- iii) There are obviously more severe patients in the female (65% severe: 35% moderate) compared to male (46% severe: 54% moderate) in the active treated group? Is this difference statistically significant? Could it affect IBS-SSS, FAS or IBS-QoL scoring?

4. Table 5-7 Microbiome and SACFA analysis.

- 1. Plot the data in bar charts or time-line changes in addition to tables."

Response: This was done and tables 2, 3, 5, 6, 8 and 10 as well as figures 2-12 were added

- "2. Are there data at 3 months after FMT?"

Response: No, faecal samples were taken only after 1 month.

- "3. Are there differences in microbiome or SCFA levels between 30 and 60g groups?"

- 4. Is there any correlation between microbial taxa and SCFA changes after FMT?"

Response: Yes, there are differences in microbiome or SCFA levels between 30 and 60g groups and yes there is a correlation between microbial taxa and SCFA changes after FMT. These observations are already published or in the way to be published. The main purpose of the present study was to investigate whether there is a gender difference in response to FMT. Thanks to the reviewer comments on the subgroup analysis that led to find a difference in the IBS-D subtype.

Minor comments

- "1. Core tip: following the text 'constipation-predominant IBS', IBS-C in parenthesis should be added.
- 2. Introduction, Line5, "Methanobacteriales methane-producing bacteria," is not a proper description, should be changed as "the Methane-producing bacteria, Methanobacteriales" or as "Methanobacteriales, the methane-producing bacteria".
- 3. Materials and Methods, Microbiome analysis and dysbiosis index Line 7: "The dysbiosis (DI)" should be "The dysbiosis index (DI)".

Response: these errors were corrected.

Science editor:

Response: All the self-cited references were proper. However, we removed references that we considered less important to accommodate the editor requirements.

“The authors need to provide the official Institutional Review Board Approval Form, and CONSORT 2010 Statement with page number.

The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);

The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;»

Response: All these were done.

«(3) The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text.»

Response: this was done.

«6 Recommendation: Transferring to the WJCC.»

Response: We are not intressted in transferring the manuscript to the WJCC. This manuscript is an invited article to WJG.