

Single Session of Fecal Microbiota Transplantation in Decompensated Cirrhosis: An open-label randomized control trial

Akash Roy

PGIMER: Post Graduate Institute of Medical Education and Research

Madhumita Premkumar

PGIMER: Post Graduate Institute of Medical Education and Research

Anima Sharma

PGIMER: Post Graduate Institute of Medical Education and Research

Nipun Verma

PGIMER: Post Graduate Institute of Medical Education and Research

Surender Singh

PGIMER: Post Graduate Institute of Medical Education and Research

Arka De

PGIMER: Post Graduate Institute of Medical Education and Research

Madhu Chopra

PGIMER: Post Graduate Institute of Medical Education and Research

Sunil Taneja

PGIMER: Post Graduate Institute of Medical Education and Research

Ajay Duseja

PGIMER: Post Graduate Institute of Medical Education and Research

Radha Krishan Dhiman (✉ rkpsdhiman@hotmail.com)

Sanjay Gandhi Post Graduate Institute of Medical Sciences

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Abstract

Background: Modulation of gut dysbiosis with Fecal Microbiota Transplantation (FMT) is a novel modality and has shown promising results in decompensated cirrhosis (DC). We explored the impact of FMT on prognostic scores, complications, ammonia levels, inflammatory markers [(Interleukin -1 (IL-1) and 6 (IL-6)], and 180-day mortality in DC.

Methods: Consecutive patients with DC (MELD12-21) were assigned to either FMT (FMT group) delivered as 30gm freshly prepared stool (from a related stool donor) homogenized in 100 ml of normal saline through a nasojejunal tube or standard of care therapy (SOC group). Outcomes were assessed on days 7, 28, 90, and 180.

Results: Eighteen patients each with comparable baseline characteristics (88.8% males; mean age, 46.12±6.23 vs. 47.0±4.54; mean CTP, 9.5±0.71 vs. 9.6±0.80; mean MELD, 16.1±1.71 vs. 1.62±1.81) were allocated to FMT or SOC. Although significant differences were noted in the CTP score on day 7 (P=0.02) and day 90 (P=0.01), MELD and MELD-Na scores were similar at all time points. A non-significant reduction in ammonia levels was seen on day 7 and day 28 (P=0.21 and P=0.17; respectively). IL-1 (P=0.01) and IL 6 (P=0.005) levels reduced significantly on day 28. New-onset variceal bleed (P=0.70), breakthrough hepatic encephalopathy events (P=0.61) and 180-day survival (HR, 2.02; 95% CI, 0.37-11.05; P=0.41). were similar. Although transient gastrointestinal side-effects were common (56.2%), no serious adverse events were noted.

Conclusion: Single session FMT in DC is safe and leads to selective improvement of CTP scores and systemic inflammatory markers but offers no survival benefit. (ClinicalTrials.gov number, NCT04842539)

Background

The natural history of cirrhosis is punctuated by the onset of decompensations in the form of ascites, variceal bleed, and hepatic encephalopathy (HE).¹ Systemic inflammation and immune dysregulation further complicate advanced cirrhosis and amplify mortality and morbidity.² Alteration in gut microbiota and consequent gut dysbiosis leads to downstream effects of aggravated systemic inflammation (SI), endotoxemia, and immune dysfunction.³ This state of enhanced SI secondary to gut dysbiosis has been proposed to play a central role in events like spontaneous bacterial peritonitis, HE, and sepsis.^{3,4} Furthermore, gut microbiota has also shown to be a significant contributor to ammoniogenesis, which has additive effects on SI neuroinflammation and mortality in cirrhosis.⁴ Previous literature has focused on enunciating this interplay and is reflected by the cirrhosis-dysbiosis ratio (CDR), which progressively worsens as patients transition from a stage of compensated (CDR=0.89) to decompensated cirrhosis (DC) (CDR=0.66).³

Modulation of gut dysbiosis with strategies such as non-absorbable antibiotics like rifaximin and probiotics has been shown to reduce endotoxemia and reduce overall disease severity in DC.^{5,6} FMT as a therapeutic modality has been convincingly used with excellent success rates for altering gut microbiota profile in *Clostridium difficile* infection.⁷ Initial experience from a few small studies indicates that FMT improves neurocognitive scores and reduces breakthrough HE episodes by altering GM and reducing SI.^{8,9,10} However, these studies have specifically focused only on the subgroup of patients with HE. Hence, in this randomized, open-labeled trial, we aimed to determine whether FMT administration in the setting of DC leads to a reduction in systemic inflammation, improvement of prognostic scores, reduction of complications, and its impact on overall survival.

Materials And Methods

Conduct of the study and study design

The study was an investigator-initiated, open-label randomized clinical trial at a tertiary care referral hospital with a specialized liver unit carried out between August 2018 to November 2019. Approval was obtained before the commencement of the study from the institutional ethics committee (INT/IEC2018/2076) and the trial was registered (ClinicalTrials.gov number, NCT04842539). The trial adhered to the CONSORT guidelines for randomized controlled trials, provisions of the Declaration of Helsinki, and good clinical practice guidelines. Informed consent was obtained prior to enrollment from each patient/relative and a stool donor after an appropriate screening. All the study authors had access to the trial data and approved the final manuscript.

Patient Selection

Consecutive inpatients and outpatients with DC were screened for enrollment eligibility. Patients satisfying the selection criteria were enrolled in the study.

Inclusion Criteria

Patients in the age group of 18-65 years with a diagnosis of DC (of any etiology) based on clinical, radiological, or histological criteria with model for end-stage liver disease (MELD scores) between 12-21 were included.

Exclusion criteria

Patients with an ongoing bacterial infection requiring antibiotics or those having received antibiotics/pre-pro biotics within the last 14 days, those with a history of significant alcohol intake in the previous two months, those with a recent (<14 days) history of spontaneous bacterial peritonitis, HE or variceal bleed, patients with a history of substance abuse or psychiatric illness, those with HIV infection, pregnant patients, patients with hepatocellular carcinoma or other known malignancy, those with history of prior liver transplantation or bariatric surgery, or those on immunosuppression, those with a history suggestive of inflammatory bowel disease, celiac disease, history of allergy to food substances were excluded.

Study objectives

Primary Objective: To assess the difference in 180-day mortality between the FMT group and the SOC group.

Secondary Objective

To assess and compare the changes in CTP, MELD, and MELD Na scores (day 28, 90, and 180) and to assess the changes in ammonia levels (day 7 and day 28) and inflammatory markers (IL-1b, IL-6,) at day 28 between FMT and SOC group.

Randomization of patients

After satisfying the selection criteria were randomized into two groups 1:1 ratio by an unrelated person using a computer-generated random number table. Allocation concealment was done using sequentially numbered opaque sealed envelopes. The physician administering FMT was aware of the treatment being administered, as the nature of the intervention meant that it was not possible to make an identical placebo.

Group 1 (FMT Group): Patients with decompensated cirrhosis who received FMT and SOC treatment for decompensated cirrhosis.

Group 2[Standard of care (SOC Group)]: Patients with DC who received only SOC treatment for decompensated cirrhosis.

SOC comprised of nutritional recommendation of a salt-restricted (<2 gm/day) and high-protein

diet (1.5-2 g/kg/day) diet with a targeted caloric intake of 35-40 kcal/kg/day. The patients underwent periodic nutrition counseling and reassessment at every visit. Anti hepatic encephalopathy measures (lactulose, rifaximin), intravenous albumin (as per standard recommendations), diuretics, beta-blockers, multivitamins, and calcium supplementation were continued as per indications and requirement. Any episode of suspected variceal bleed was managed with proton pump inhibitors, vasoconstrictors, and endoscopic intervention as indicated.

Stool Donor Selection:

Stool donor selection was done in a two-step process. Firstly, identified family members willing to become a stool donor were interviewed to assess history and risk factors for eligibility for being an FMT donor as per recommended guidelines.¹¹ In brief, donors, were excluded if they had abdominal complaints, history of recent abdominal infections or been on antibiotics within the previous two months, had a history of chronic gastrointestinal diseases, history of luminal gastrointestinal surgery, history of any malignancy, autoimmune/atopic or neurological conditions, history of extensive travel history predisposing factors for potentially transmittable diseases, occasional or chronic alcohol intake or other substance abuse or had any state of primary or secondary immunosuppression. Once found suitable, the donor underwent detailed stool, blood, and urine tests to ensure that known transmissible diseases would not be passed along to recipients through FMT as per laid-out guidelines.¹¹

Preparation of Donor Stool

Donors collected and submitted a fresh stool sample on the day of FMT after arriving at the hospital in sterile plastic collection containers. All personnel in stool specimen preparation wore personal protective equipment and performed the procedure in a pre-designated zone. All stool samples were obtained at least 6 hours before the procedure. Stool specimens with a weight of ~30 g were taken as adequate. 100 mL of sterile normal saline was added to the stool sample and homogenized with an electronically operated blender for three cycles of thirty seconds each. The homogenous suspension was then filtered with filter paper and tea strainers 3-4 times until the filtrate was devoid of roughage.

Pre FMT Preparation

Participants randomized to the FMT group received pretreatment oral antibiotics (metronidazole 400 mg three-time daily, ciprofloxacin 500 mg twice daily, and amoxicillin 500 mg three times daily) for five days to reduce the host gut bacterial load and enable donor microbiome colonization.⁸ Lactulose and rifaximin were continued for all patients as per indication. All antibiotics were discontinued 12 hours before FMT to prevent modulation of administered FMT. Participants in the SOC group did not receive this pre-therapy antibiotic but otherwise had the same follow-ups post-randomization.

The FMT Procedure

In the FMT procedure, a 100 ml volume of strained and filtered stool was delivered through a nasojejunal (NJ) tube in two delivery sessions spaced 10 minutes apart in volumes of 50 ml each. The recipient patient was kept nil per oral for at least 4 hours before the stool instillation. The NJ tube was flushed with normal saline (50mL) after the stool instillation. The patients were allowed to consume a liquid diet two hours after the procedure. All patients continued SOC therapy, as advised in the management of DC.

Clinical and Laboratory Assessments

Clinical examination included a detailed evaluation of vital parameters, general physical examination, and a systemic examination. Laboratory investigations included a hemogram, renal and liver function tests, and a complete

coagulogram. Liver disease severity was assessed using the Child–Turcotte–Pugh (CTP), MELD, and MELD-Sodium (MELD Na) scores. Blood samples from a peripheral vein were taken at baseline and days 7, 28, 90, and 180. Fasting ammonia Checker II (Daiichi Kagaku Co Ltd, Kyoto, Japan) using finger-prick capillary blood and measured at baseline, day 7, and day 28.

Assessment of Pro-inflammatory Cytokines

Cytokines (Interleukins IL-1 and IL6) were measured in plasma derived from patients using Human beta PicoKine ELISA kits (Boster Biological Technology) according to the manufacturer's protocol. The plate was read at 450 nm. Absorbance was converted to picograms per milliliter using a standard curve prepared with recombinant human IL1, IL6. Measures were taken at baseline and 28 days post-FMT

Follow Up

Follow-up of patients was done on days 7, 28, 90, and 180 in both groups. During follow-up, patients were evaluated for clinical parameters, routine biochemical monitoring, and inflammatory markers.

Adverse Events

All adverse events were recorded and graded according to Common Terminology Criteria for Adverse Events (CTCAE). Any event that resulted in death was life-threatening, required inpatient hospitalization, extended an ongoing hospital stay, or interfered substantially with normal life functions was considered a serious adverse event.

Statistical Analysis

The results are expressed as number (proportion) for categorical data, mean (95% Confidence Interval; CI or standard deviation; SD) for normally distributed numerical data, or median (range) for skewed numerical data. Comparisons between groups for numerical data were performed using student's t-test or the Mann–Whitney U test. For categorical data, the chi-square test or Fisher's exact test were applied. For intra-group comparisons, a repeated measures Analysis of Variance (RMANOVA) with a Greenhouse-Geisser correction was performed. A value of $P < 0.05$ (two-tailed) adjusted for multiple comparisons was taken as significant. The in-hospital survival curves were made by the Kaplan-Meier method and compared with the Log-Rank test. All statistical tests were done by Microsoft Excel and SPSS Software version 18 for Windows.

Sample size calculation

The only previous study which has looked at the impact of FMT on the survival of patients with liver disease, albeit in a population of severe alcoholic hepatitis, found a 75% survival in the FMT group and a 29% survival in the SOC group at 90 days.¹² However, given the exploratory endpoints of this trial in patients with decompensated cirrhosis, a population which has previously not been looked at, as well as an unexpectedly low acceptance rate of FMT as a therapeutic modality in our population, we could enrol only 18 patients in each group in the pre-specified time period.

Results

Study patients

Seventy-nine patients with decompensated cirrhosis aged between 18-75 years with MELD scores between 12 and 21 were screened. The baseline characteristics of all patients are shown in Supplementary Table 1. After applying the appropriate selection criteria, 43 patients were excluded, and the remaining 36 were included in the study. The flow diagram of patients enrolled in the study is shown in Supplementary Fig 1. The most common cause of exclusion was a

refusal to give consent for FMT (76.74%). The clinical and demographic characteristics of the patients included in the study are shown in Table 1. Both the groups were similar in their baseline characteristics except for hemoglobin levels ($p=0.03$)

Evaluation of variability in biochemical parameters and prognostic scores

As our study aimed to seek differences both within and between each group at multiple days of analysis ranging from day 0 to day 180, we performed RMANOVA to determine differences in mean values at each day within each arm as well as compare the groups at specific time points. There was a significant improvement in bilirubin ($P=0.001$) and albumin ($P=0.01$) levels within the FMT arm. However, on intergroup comparisons, no significant change was observed in any biochemical parameters except for albumin levels at day 28.

In the analysis of the prognostic scores, the two arms behaved differently. In the FMT arm, the CTP score showed significant improvement over 180 days ($p=0.01$) and also differed significantly between the groups at day 7 ($p=0.02$) and day 90 ($p=0.01$). On the contrary, the MELD and MELD-Na scores showed a worsening in the SOC group. However, on intergroup comparisons, there were no significant differences between the MELD/MELD-Na scores at any time point between the two groups (Table 2 and Supplementary figure 2)

Changes in prognostic scores from baseline (Δ scores):

We analyzed the changes in the prognostic scores as differences from the baseline score assigned as Δ (Day 0 score – Corresponding day score) to evaluate differences in corresponding changes during follow up. In the analysis of the Δ scores, our results showed a significant difference in the Δ CTP score at day 7 ($P=0.02$) and day 90 ($P=0.01$). There was no significant difference with respect to the other scores on any day during follow-up (Supplementary Table 2).

Dynamic changes in Ammonia levels

The dynamic changes in ammonia levels were assessed in each arm on sequential follow-up at days 0, 7, and 28. There was an overall reduction in ammonia levels in the FMT arm on day seven, which was maintained on day 28. However, the differences in the changes in ammonia levels in each arm did not reach statistical significance. The differences between Δ Ammonia levels (Ammonia levels at Day 1 – Ammonia levels at day 7 and day 28, respectively) were assessed and not found to be statistically different (Table 3).

Survival analysis

We followed patients in each arm for 180 days or death, whichever was earlier. In the FMT arm, 16 patients were alive at the end of 180 days, while 14 patients were alive in the SOC arm at the end of 180 days. The cumulative probability of 180-day survival was not significantly different between the two groups (88.8% vs. 77.7%; $P=0.65$). Using the log-rank (Mantel-Cox) test, there was no significant differences in survival between both arms ($P = 0.40$, HR = 2.02, 95% CI = 0.37-11.05). The mean overall survival in the entire population was 169.72 ± 4.56 days. The mean overall survival was 171.78 ± 5.83 days in the FMT arm, while in the SOC arm, it was 167.67 ± 6.94 days. The Kaplan-Meier survival analysis curve for overall survival at 180 days is shown in Fig 1. There were no differences in breakthrough HE or variceal bleed (Supplementary figure 3). There were also no differences between hospitalization events between the two groups ($P=0.78$)

Assessment of cytokine levels in response to FMT

Interleukin-1 (IL-1)

The interleukin levels of both groups at baseline were comparable. There was a significant reduction in the IL-1 levels on day 28 compared to baseline in the FMT arm, whereas there was a rise in the levels of IL-1 in the SOC group (P=0.01). The Δ IL 1 values (IL-1 at baseline –IL at day 28), however, were not significantly different in both groups (p=0.32).

Interleukin 6 (IL-6)

There was a significant reduction in the IL-6 levels on day 28 compared to baseline in the FMT arm, whereas there was a rise in the levels of IL-1 in the SOC group (P=0.005). The Δ IL 6 values (IL-6 at baseline –IL-6 at day 28), however, were not significantly different in both groups (P=0.37). The results of the variation in interleukin levels are shown in Figure 2.

Adverse events associated with FMT administration:

. The most common treatment-related reported adverse event was nausea (56.25%) followed by gastroesophageal reflux (44.44%), bloating sensation (33.33%), and flatulence (33.33%) (Table 4). No serious adverse events (SAE), including aspiration pneumonia, spontaneous bacterial peritonitis, or bloodstream infection were observed.

Acceptance of FMT as a therapeutic modality

41.7% up had an up-front refusal to participate in the study, primarily due to preconceived notions and unwillingness to accept fecal-based therapy.

Discussion

Previously the use of FMT in DC has mostly been evaluated in selected patients with recurrent HE.^{8,10} We demonstrated the effects of administering a single session of FMT in an exploratory cohort, encompassing the entire spectrum of DC. Although there was a significant improvement in bilirubin and albumin levels within the FMT arm, intergroup variations were not significant at any time point (except for albumin levels at day 28). The only previous study which has evaluated changes in bilirubin levels with capsule-based FMT also found no significant differences between FMT and SOC arms (1.2 ± 0.80 vs. 1.4 ± 0.80 ; p=0.53).¹⁰ Both previous studies analyzing FMT's role in DC failed to observe any differences in albumin levels.^{8,10} Sequential creatinine and INR were also similar between the two groups, which too is in concordance to a previous study.⁸

FMT significantly improved the CTP score at specific time points (days 7 and 90) . In contrast to the CTP score, no significant differences in MELD and MELD Na scores were observed. Bajaj et al. in a previous study using oral capsule FMT in patients with HE, also found no differences in the MELD scores at day 30 (8.7 ± 2.9 vs 11.3 ± 3.9 ; P=0.11).¹⁰ In another study where FMT was delivered as an enema, the same group, did not find a difference between the MELD scores changes between day 0 and day 35 (0.1 ± 2.0 vs. -0.2 ± 2.7 ; p=0.78).⁸ On the contrary, Mehta et al. have shown significant improvement in both CTP and MELD scores between baseline and week 20 [P=0.005; P= 0.008, respectively].⁹ However, this latter study had an intrinsic limitation of not having a comparative control group. The differences between these studies possibly reflect differences in the baseline MELD scores. Whereas the studies by Bajaj et al.^{8,10} selectively enrolled patients at lower MELD scores, the other study had a higher baseline MELD. It is important to note that while we noted changes in the CTP scores, similar changes were not replicated in MELD and MELD Na scores. This probably is related to differences in the individual parameters assessed by these scores and variations in serum albumin levels due to unmatched albumin infusions.

We observed a non-significant reduction in the ammonia levels both at day 7 and day 28 after FMT. Mehta et al. have previously reported a significant reduction in ammonia levels measured at baseline and 20 weeks after administration of a single session of FMT.⁹ It may be of interest to analyze such changes in a larger, more homogenous population.

We observed significant reductions in the levels of both IL 1 and IL 6 with FMT. Previous studies have assessed the role of gut-based therapies like VSL#3 and rifaximin and showed a reduction of plasma inflammatory cytokine levels.^{13,14} Ours is the first study that has looked at changes in cytokine levels after administration of FMT and based upon our results FMT possibly has a role in reducing systemic inflammation, although its clinical implications need to be evaluated further.

We did not observe any differences in the events of incident HE or variceal bleed or hospitalization rates. One of the most attractive applications of FMT in previous studies has been its postulated role in the prevention of HE recurrence both in the short and the long term.^{8,15} Although our study did not establish such differences, it is essential to state that differences in the study population's inherent characteristics may account for such variability.

Overall survival at six months was similar in our study. No studies have individually looked at overall survival differences after FMT administration to date, although studies have shown trends towards decreased hospitalization rates.^{8,10} Given the natural history of decompensated cirrhosis, we need further appropriately powered studies with a longer duration of follow-up to ascertain its impact on long-term survival.

Finally, there have been recent reports concerning the development of multi-drug-resistant-organism infections after FMT.¹⁶ In our study, we noted only transient gastrointestinal adverse events, and no SAE was observed. Bajaj et al., in their previous studies, also did not observe any increased incidence of SAE in patients with DC.^{10,15} A stringent selection and screening of donors are imperative to ensure the prevention of transmission of such infections, and future studies for determining the adequacy of screening are warranted.

Limitations

Our study has several limitations that possibly have an impact on outcomes. Firstly, with a relatively small sample size of eighteen patients in each group, our study is not adequately powered to ascertain significant differences in clinical endpoints. However, given the novel nature of the use of FMT in DC, this study serves as preliminary data for larger randomized trials. Secondly, the unblinded nature of this study is a significant limitation. However, given the difficulty in preparing a matched placebo, it is perhaps improbable at the current stage to devise trials with such a matched placebo arm. Thirdly, an integral part of validating response to FMT is simultaneous documentation of changes in gut microbiota and relative abundance of engrafter operational taxonomic units, which were not a part of this study. Lastly, we used only a single session of FMT, the effects of which may not be long-lasting, and future studies with multiple schedules of FMT are warranted to determine sequential changes.

Conclusion

In a stable population of DC, FMT is safe. There is an improvement in selected prognostic scores, which, however, does not translate into an improvement in 180-day survival. FMT leads to a non-significant reduction in ammonia levels. Inflammatory cytokines (IL-1 and IL-6) show a significant reduction after FMT administration.

Abbreviations

AKI	Acute Kidney Injury
ALT	Alanine Transaminase
ALP	Alkaline Phosphatase
AST	Aspartate Transaminase
CDR	Cirrhosis-Dysbiosis-Ratio
CTP	Child-Turcotte-Pugh
CTCAE	Common Terminology Criteria for Adverse Events
DC	Decompensated Cirrhosis
FMT	Fecal Microbiota Transplantation
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HE	Hepatic encephalopathy
HIV	Human immunodeficiency virus
IL	Interleukin
INR	International Normalized Ratio
LGG	<i>Lactobacillus rhamnosus</i> GG
MELD	Model for end-stage liver disease
MELD Na	Model for end-stage liver disease Sodium
NAFLD	Non-alcoholic fatty liver disease
SAE	Serious Adverse Events
SOC	Standard of Care

Declarations

Data availability: Available.

Animal Research (Ethics): Not applicable

Consent to participate (Ethics): Informed consent obtained from all participants

Consent to publish (Ethics): Obtained

Plant Reproducibility: Not applicable

Clinical trial registration: ClinicalTrials.gov number, NCT04842539

Author contribution: AR: Conceptualization, data curation, writing original draft; RKD: Conceptualization, methodology, writing- review and editing; MPK: Project administration, resources, writing- review and editing; NV: Visualization, writing- review and editing; ArD Supervision, resources; AS Investigation; SS: Project administration MC: Resources; ST Supervision, writing- review and editing; AD Supervision, writing- review and editing

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Declaration of presentations and awards related to this research:

The study was presented at The Liver Meeting, American Association for the Study of Liver Disease 2020, and was judged as the Best of The Liver Meeting's in the Gut Liver Axis and Microbiome category.

Dr. Akash Roy received the **Cheung Family Memorial Travel Award** from the American Association for the Study of Liver Disease for this study at The Liver Meeting, 2020, AASLD.

Dr. Akash Roy was also awarded **The Professor Mindie H. Nguyen Award for Outstanding Clinical Research by an Early Career Investigator** for this work.

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Tables

Table 1: Baseline Characteristics of the Patients

Characteristics	FMT group (N=18)	SOC group (N=18)	P-value
Demographic and Anthropometric Parameters			
Age (years)	46.3 (43.29-49.37) *	46.8 (45.11-48.66)	0.74
Male gender, number (%)	16(88.88%) **	16(88.88%)	1
Height (cm)	167.5(163.81-171.18)	169.3(165.55-173.15)	0.72
Weight (kg)	66.1(61.53-70.68)	66.2(62.53-70.02)	0.95
BMI Kg/M ²	23.4(22.09- 24.86)	22.8(21.44-24.26)	0.49
Aetiology of Cirrhosis			
Alcohol	13 (72.2%)	13(72.2%)	1
HBV	2(11.1%)	1(5.6%)	0.55
HCV	1(5.6%)	2(11.1%)	0.55
NAFLD	2(11.1%)	2(11.1%)	1
Decompensations at baseline			
Ascites only (A)	6(33.3)	6(33.3)	1
HE only (B)	3(16.7)	3(16.7)	1
Variceal Bleed Only(C)	0	1(5.5)	1
A+B	4(22.2)	4(22.2)	1
A+C	5(27.7)	3(16.7)	0.69
B+C	0	0	1
A+B+C	0	1(5.6)	1
Biochemical Parameters			
Haemoglobin (gm/dl)	10.6 (9.94-11.35)	9.7(9.24-0.24)	0.03
TLC (10 ⁹ /L)	6.89(5.88-7.98)	7.6(6.47-8.72)	0.33
Platelets (x 10 ³ /mm ³)	72.5(57.14-88.03)	70.7 (58.05- 83.49)	0.85
Serum Bilirubin (mg/dl)	3.0(2.56-3.51)	2.9(2.62-3.21)	0.68

AST (IU/L)	55.5(45.22-73.43)	49.5(44.28-61.55)	0.19
ALT (IU/L)	39.2 (31.33-55.67)	38.1(32.22-46.33)	0.08
Albumin (g/dl)	2.7(2.63-2.93)	2.79(2.69-2.89)	0.94
INR	1.6(1.52-1.74)	1.6(1.51-1.70)	0.68
Serum Creatinine (mg/dl)	1.02(0.93-1.13)	1.0(0.96-1.14)	0.67
Sodium (mEq/L)	132.2 (130.11-135.66)	133 (130.23-137.43)	0.29
Potassium (mEq/L)	4.1(3.61-4.52)	3.8(3.21-4.49)	0.40
Mean arterial pressure(mmHg)	76.7(66.87-82.44)	73.8(65.67-81.98)	0.33
Arterial Ammonia (mmol/L)	83.0(68.34-97.65)	80.5(63.68-97.43)	0.81
Prognostic Scores			
CTP	9.5(9.01-9.91)	9.6(9.30-9.91)	0.68
MELD	16.1(15.12-16.81)	16.2(15.31-16.73)	0.94
MELD Na	16.5(15.90-17.09)	16.3(15.69-16.97)	0.68

NOTE. Data are expressed as *means (95% CI) or **N (%).

BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, non-alcoholic fatty liver disease; TLC, total leucocyte count; ALT, alanine transaminase; AST, aspartate transaminase; INR, international normalized ratio; CTP,, Child Turcotte Pugh score; MELD=model for end-stage liver disease; MELD-Na=MELD-sodium,

Table 2: Showing variations in parameters within each arm at follow up with repeated-measures ANOVA

Characteristics	Group	Day 0	Day 7	Day 28	Day 90	Day 180	P** value
Hemoglobin (gm/dl)	FMT	*10.6±1.42^a	10.6±0.98^a	10.5±0.98^a	10.3±1.31	10.0±0.74	0.05
	SOC	9.7±1.03^a	9.9±0.74^a	9.7±1.05^a	9.8±0.60	9.6±0.79	0.35
TLC (10 ⁹ /L)	FMT	6.8±2.03	6.4±2.29	7.9±1.19	7.8±3.20	6.8±1.71	0.08
	SOC	7.6±2.2	6.9±1.5	7.6±1.31	7.1±2.47	7.6±3.19	0.43
Platelets(x10 ³ /cumm)	FMT	72.5±31.06	83.6±36.61	70.4±30.59	78±31.04	89.1±32.82^b	0.50
	SOC	70.7±25.57	80.53±20.15	76.9±25.33	68.6±21.72	59.2±33.11^b	0.06
Bilirubin(mg/dl)	FMT	3.0±0.95	3.0±0.86	2.9±0.99	2.8±0.88	2.6±0.86	0.001
	SOC	2.9±0.62	2.9±0.63	2.9±0.55	3.3±1.59	3.0±0.74	0.38
AST (IU/L)	FMT	67.2±38.82	59.7±25.10	59.8±18.87	54.9±17.66	55.7±18.60	0.08
	SOC	54.1±15.31	51.9±11.96	53.1±12.85	52.7±15.82	52.6±10.45	0.24
ALT (IU/L)	FMT	48.8±28.97	40.2±13.56	40.3±11.56	38.1±9.48	36.3±12.54	0.23
	SOC	36.1±9.38	34.8±7.75	36.9±7.26	39.8±11.51	34.31±4.52	0.52
Albumin(g/dl)	FMT	2.7±0.30	2.8±0.36	3.0±0.29^c	2.9±0.37	2.9±0.13	0.01
	SOC	2.7±0.21	2.8±0.24	2.8±0.16^c	2.8±0.27	2.8±0.25	0.71
INR	FMT	1.6±0.22	1.6±0.24	1.7±0.36	1.6±0.24	1.6±0.26	0.12
	FMT						
	SOC	1.61±0.18	1.69±0.17	1.67±0.23	1.73±0.36	1.8±0.36	0.09
	SOC						
Creatinine(mg/dl)	FMT	1.02±0.23	1.01±0.17	1.01±0.21	1.06±0.25	0.97±0.18	0.90
	SOC	1.05±0.17	1.03±0.13	1.03±0.13	1.13±0.32	1.21±0.55	0.29
CTP score	FMT	9.5±0.98	9±0.68^b	9.1±0.98	9.1±0.83^c	9.1±0.7	0.01
	SOC	9.6±0.60	9.6±0.90^b	9.5±0.70	9.8±0.99^c	9.7±1.04	0.62
	SOC						
MELD score	FMT	16±1.41	16.05±1.39	16.3±2.24	16.5±2.09	16.1±1.51	0.58
	SOC	16±1.41	16.05±1.34	15.72±1.40	17±2.82	16.9±2.56	0.03
MELD Na score	FMT	16.5±1.21	16.7±1.44	16.6±2.45	16.6±1.68	16.3±1.44	0.71

NOTE. Data are expressed as * means±sd; where sd=standard deviation; ** p values were calculated using Analysis of variance (ANOVA) with Greenhouse-Geisser correction

TLC, Total leucocyte count; ALT, Alanine transaminase; AST, Aspartate transaminase; INR, International normalized ratio; CTP=Child Turcotte Pugh score; MELD=model for end-stage liver disease; MELDNa=MELD sodium

^{aa}P=0.03, ^{bb}P=0.02, ^{cc}P=0.01, ^{bb}P=0.02, ^{bb}P=0.02,

Table 3: Dynamic changes in ammonia levels in both arms

Variable	FMT group (N=18)	SOC group (N=18)	P-value
Ammonia Levels Day 0	*83.0(68.34-97.65)	80.5(63.68-97.43)	0.81
Ammonia Levels Day 7	77.0(68.09-86.03)	83.5(69.93-97.18)	0.40
Ammonia Levels Day 28	77.2(67.20-87.38)	81.40(63.61-99.18)	0.66
Δ Ammonia Day 7	6.21 (-4.78-17.31)	0.37(-13.50- 14.27)	0.48
Δ Ammonia Day 28	7.29 (-3.55-18.13)	3.46(-18.87- 25.81)	0.73

Note Data are expressed as *means (95% CI) ;Ammonia levels are in mmol/L

Table 4: Adverse events related to FMT in decompensated cirrhosis

Reported Events	CTCAE# Grade	Number (%)	Time of reporting
Nausea	Grade I (all)	9(56.25%)	On day of FMT*
Gastroesophageal Reflux	Grade I (5/8) Grade II (3/8)	8 ((44.44%)	Up to 72 hours after administration of FMT
Bloating	Grade I (all)	6 (33.33%)	Up to 72 hours after administration of FMT
Flatulence	Grade I(all)	6(33.33%)	Up to 72 hours after administration of FMT
Transient fever	Grade I(all)	3(16.66%)	Within 48 hours of FMT administration
Vomiting	Grade I (all)	4(22.22%)	On day of FMT
Abdominal pain	Grade 1 (all)	2(11.11%)	On the day of FMT

Figures

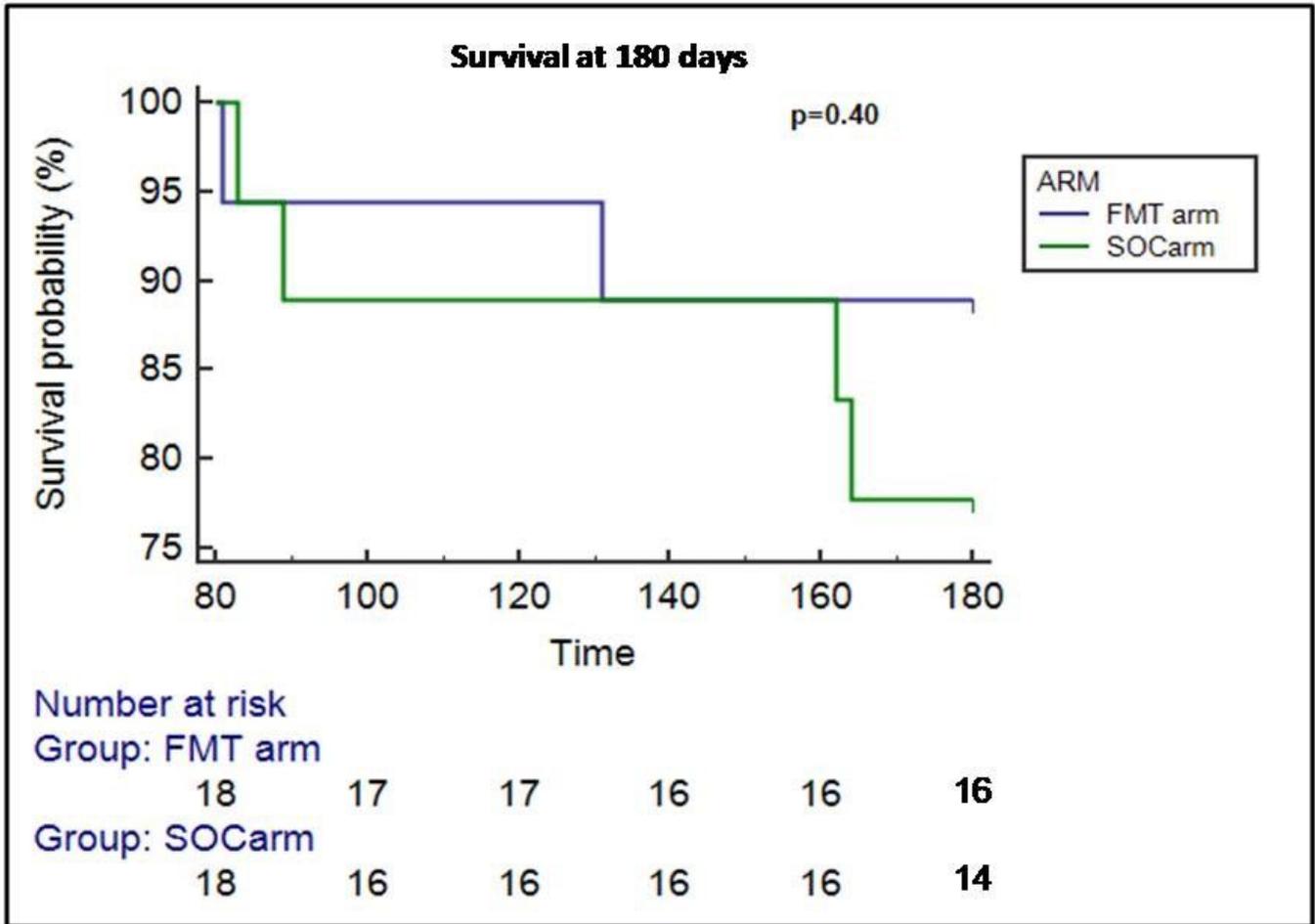


Figure 1

Kaplan-Meier curve showing survival in the FMT and SOC arm

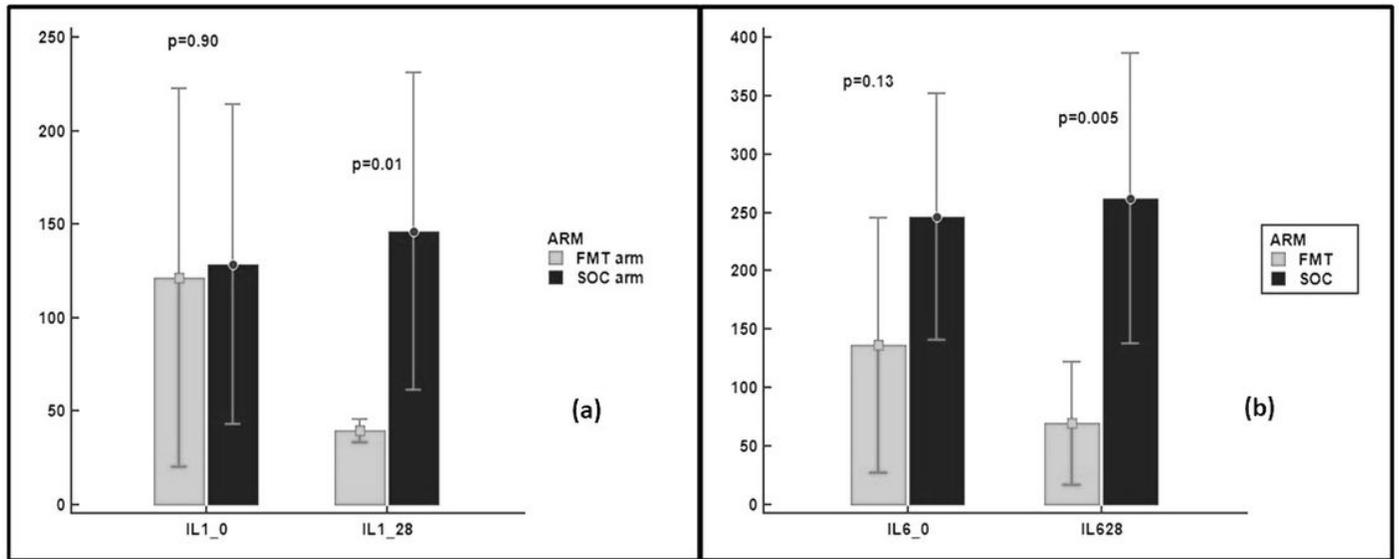


Figure 2

(a) Showing variations of Interleukin 1 levels at baseline and day 28 (b) Showing variations of Interleukin 6 levels at baseline and day 28

Supplementary Files

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