Fecal microbiota transplantation in hepatic encephalopathy : a review of the current evidence and future perspectives

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Abstract

Hepatic encephalopathy (HE) is a leading cause of hospitalization and morbimortality in advanced cirrhosis with limited therapeutic options available. Given the paramount role of gut microbiota in HE, and the efficacy of fecal microbiota transplantation (FMT) in other diseases, this review intends to summarize the evidence supporting the safety, efficacy and future perspectives of FMT in HE. Current evidence, despite being scarce, points towards FMT being a safe, effective and tolerable procedure in HE. Some unanswered questions remain about the optimal dose, the administration route, the long term effects and the selection of the optimal donor. Future trials, some of which are already underway, will provide us additional evidence and hopefully the necessary answers. (*Acta gastroenterol. belg.*, 2021, 84, 87-90).

Keywords : Hepatic encephalopathy, fecal microbiota transplantation, gut microbiome, cirrhosis.

Introduction

Hepatic encephalopathy (HE) is one of the leading causes of hospitalization and one of the most debilitating complications of cirrhosis or portosystemic shunting, affecting the quality of life of both patients and caregivers. Additionally, it is associated with a significant health-care financial burden due to cognitive impairment and repeated hospitalizations (1).

Overt HE occurs in up to 14% of patients by the time of the diagnosis of cirrhosis, increasing up to 21% in decompensated cirrhosis. The cumulative incidence of overt HE is 40% during the clinical course of the disease, often relapsing (1). The mortality of HE is around 5-27% during hospitalization, increasing up to 50% at one year of follow-up (2,3).

Although the pathogenesis of HE isn't completely understood and is probably multifactorial, there is growing evidence supporting a central role of gut microbiota. In cirrhosis, a reduction of beneficial commensal bacteria (ex : *Ruminococcaceae* and *Lachnospiraceae*) and an increase of non-autochthonous bacteria (ex : *Streptococcaceae* and *Enterobacteriaceae*) has been previously demonstrated (4,5,6). This results in a microbiome imbalance known as "cirrhosis dysbiosis ratio", which is associated with an increased model for end stage liver disease (MELD) score (5). It is believed that ammonia, a neurotoxin produced by urease-containing bacteria, through a combination of decreased metabolism in the diseased liver, decreased skeletal muscle clearance and portosystemic shunting, penetrates the blood-brain

Figure 1. — Gut-liver-brain axis and hepatic encephalopathy

barrier and is the main contributing factor for HE. There is also a role for local and systemic inflammation and endotoxemia, precipitated by bacterial translocation (7,8). These mechanisms are outlined in figure 1. The gut-liver axis results in a complex interaction between liver function and gut microbiome and is fundamentally altered in cirrhosis. One of the proposed main mechanisms of dysbiosis is the decrease of bile acid production (due to liver insufficiency), which in turn has a direct effect over gut microbiome, favoring non-autochthonous

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Submission date : 27/07/2020

Acceptance date : 09/10/2020

bacteria. Other factors such as diet, inflammation, portal hypertension and drugs (antibiotics and proton pump inhibitors) also play a part in dysbiosis. On the other hand, the “good” bacteria are critical in maintaining an intact gut barrier and reducing bacterial translocation associated with advanced cirrhosis (7,9).

The current standard of care (SOC) treatment for HE are non-absorbable disaccharides (lactulose and lactitol) and non-absorbable antibiotics (rifaximin) (1). Non-absorbable disaccharides work through several mechanisms, such as reducing the absorption of ammonia due to a direct laxative effect and by acidifying the colon, but also working as a pre-biotic, allowing for the proliferation of non-urease containing commensal bacteria, which metabolize these disaccharides into short-chain fatty acids. Rifaximin reduces pathological bacteria load but also changes their virulence and behavior to more beneficial effects (8,7).

Fecal microbiota transplantation (FMT) is a highly effective therapy in recurrent *Clostridium difficile* infection (10,11,12). It is currently under investigation in other diseases in which gut microbiota also has a pivotal role such as irritable bowel syndrome (13,14,15), intestinal colonization by multi-drug resistant microorganisms (16,17,18) or ulcerative colitis (19) with promising results.

Given the current evidence of the paramount role of gut microbiota in HE and the limited therapeutic options available that already target the gut microbiome, the purpose of this review is to summarize the available evidence supporting the safety, efficacy and future perspectives of FMT in HE.

Efficacy of FMT in HE

The first case report of FMT in HE was published by Kao et al (20) in 2015. This case reports a patient with grade I-II (West-Haven criteria [WHC]) HE previously treated with lactulose and rifaximin. As the patient could no longer afford rifaximin, a FMT delivered by enema from an unrelated donor was proposed. The patient performed 4 sessions on a weekly basis, with marked improvement in subjective and objective parameters but relapsing to baseline at week 14. This data suggested a beneficial but transient effect of FMT in HE. Other case report (21) available only as an abstract described a patient with refractory WHC grade 4 HE, despite SOC treatment. He was treated with a daily FMT (healthy family member donor), by enema, for 5 days, with complete improvement of HE. Unfortunately, no follow-up was described. No information was provided on the volume of FMT used on both case reports.

In a case series (22), 10 patients with WHC grade II-IV recurrent HE, treated with SOC therapy for HE, were subjected to FMT via colonoscopy after 5 days of broad spectrum antibiotics. No information on FMT volume was reported. Healthy donors, selected by the patient or their caregivers, were screened and treated with single

dose albendazole prior to donation. Sustained clinical response at week 20 was observed in 6 patients, with no recurrence of HE. Furthermore, a decrease in median MELD score (18 vs. 15 ; $p < 0.01$) and median Child-Pugh score (9.5 vs. 8 ; $p < 0.01$) was observed in this cohort. Microbiota changes were not analyzed and no information on long term follow-up was provided.

The first randomized, open-label trial was published by Bajaj and colleagues in 2017 (23). In this trial, a single non-related donor was rationally selected to have higher relative abundance of beneficial commensal bacteria, namely *Lachnospiraceae* and *Ruminococcaceae*. All patients enrolled were under SOC treatment for HE and proton pump inhibitors, which they maintained for the duration of the trial. A total of 20 patients with similar baseline characteristics were randomized to a SOC arm and a SOC plus a single FMT (90mL by enema) arm, each one with 10 patients. The follow-up was 5 months. All FMT patients received broad spectrum antibiotics for 5 days previous to the procedure (discontinued 12h before FMT). The primary endpoint was safety (compound endpoint of death, hospitalizations, emergency room visits or infections) and secondary endpoints were cognitive function, MELD score and microbiota changes. At the end of follow-up, there was a significant difference in HE episodes between both groups (0 in FMT vs. 6 in SOC ; $p = 0.03$). There was significant improvement in cognitive function in the FMT group compared to baseline (Stroop test $p = 0.04$ and psychometric hepatic encephalopathy (PHES) score $p = 0.01$). There were no significant differences in MELD scores between groups. A relative increase in *Lachnospiraceae* and *Ruminococcaceae* was observed in the FMT arm compared to the SOC arm. The previous findings were further expanded (24) by increasing the follow-up of these patients for at least 12 months and up to 15 months. The authors reported an acceptable long-term safety profile for the FMT group. There were significantly less hospitalizations (10 vs 1 ; $p = 0.05$) and HE events (8 vs 0 ; $p = 0.03$) in the SOC plus FMT arm. Cognitive function remained significantly better in the FMT group. Although these results are very promising, this study has some important limitations, namely pre-treatment with antibiotics which also influence the microbiome, leading to a possible bias of the precise role of FMT ; optimal dosing, donor selection and delivery methods for FMT in HE are still unknown as there is insufficient data, which might limit the generalization of this study ; absence of placebo control group with sham FMT ; small sample size including patients with a relatively preserved liver function.

More recently, a randomized and placebo-controlled trial (phase 1) was published by Bajaj et al. (25) with a study design similar to the abovementioned randomized trial. Patients with recurrent HE under SOC treatment and MELD score ≤ 17 were enrolled. A single non-related donor was used and the FMT delivery method to the patients consisted in oral capsules (single ingestion

Table 1. — Ongoing registered clinical trials of fecal microbiota transplantation in hepatic encephalopathy (www.clinicaltrials.gov)

NCT number	Study arms	Study design	Primary endpoint	Patients, n	Follow-up
NCT03796598	I – Capsule+Enema FMT II – Capsule FMT+Enema placebo III – Capsule placebo+Enema FMT IV – Capsule+enema placebo Once, day 30	Randomized, controlled, double blinded	Serious adverse events	100	6 months
NCT03420482	I – Capsule FMT II – Capsule placebo Day 1, 2, 7, 14, 21	Randomized, controlled, double blinded	Cognitive performance (measured by PHES) at week 4	30	8 weeks
NCT03439982	I – Enema FMT Week 0, 1, 2, 3, 4	Phase 1 and 2 unblinded trial	Time until overt HE after intervention	30	9 weeks
NCT02255617	I – Enema FMT Week 0, 1, 2, 3, 4	Phase 1 and 2 unblinded trial	Time until overt HE after intervention	4	6 months
NCT04155099	I – High dose lyophilized capsule FMT II – Low dose lyophilized capsule FMT III – Placebo capsule Twice/week, 4 weeks	Randomized, controlled, double blinded	Cognitive performance (measured by Stroop test) at 1 month	75	12 months
NCT02862249	I – FMT via gastroscopy II – Placebo via gastroscopy	Randomized, single blinded	Safety, tolerability and feasibility	32	18 months

of 15 capsules), while the control group received placebo capsules. The primary outcomes were safety and tolerability of FMT (determined by serious adverse events, requiring hospitalization) and secondary outcomes were other adverse events (not requiring hospitalization), changes in microbiota, changes in cognitive function and inflammation markers. A total of 20 patients were enrolled, with similar baseline characteristics, half in each group, as the authors calculated this sample had enough power to test safety outcomes. At the end of the follow-up period (5 months), there were less serious adverse events ($n=11$ vs. $n=1$, $p<0.05$) and less HE events ($n=7$ vs. $n=1$, $p>0.05$) in the FMT arm compared to the placebo arm. Notably, the HE event in the FMT group was considered unrelated, as it occurred after a transjugular intra-hepatic portosystemic shunt procedure. Although this study was not powered for FMT efficacy, a trend of decreased hospitalizations and decreased severe adverse events was observed for the FMT arm. Patients in the FMT arm had an improvement in the cognitive function as objectively assessed with the increased results in the Stroop test at the end of the study compared to baseline. This outcome was not observed in the placebo arm. Patients in the FMT group had higher *Lachnospiraceae* compared to placebo. When analyzing duodenal mucosa, the FMT group had a higher concentration *Ruminococcaceae* and *Bifidobacteriaceae* and a reduction in *Streptococaceae* and *Veillonellaceae*, when comparing pre and post FMT. These changes in microbiota were accompanied by decreased intestinal inflammation. Nevertheless, this study also had several limitations : the small sample size limited the conclusions about the efficacy of the oral route for FMT ; rifaximin was not discontinued, which might affect the conclusions about FMT ; lastly, all patients were on proton-pump inhibitors, a medication known to influence gut microbiota.

Safety of FMT in HE

Short term safety data for FMT is already available in the setting of recurrent *Clostridium difficile* treatment (12), even in immunocompromised patients (26). In this setting, most adverse events reported were mild and self-limited. In HE, the data presented in both studies by Bajaj JS (23,25) seems reassuring regarding short-term safety. Of the 20 patients included in both studies, only one developed a severe adverse event. Nevertheless, it was considered unrelated to FMT by an independent assessment team. Despite the promising results and the currently known safety of FMT performed in other settings, more evidence from randomized controlled trials is warranted to determine the safety of FMT in HE.

Long term safety data for FMT is still lacking and there is concern that gut microbiota may transfer unknown infectious pathogens or even induce chronic diseases phenotypes, including obesity, diabetes, colon cancer, irritable bowel syndrome, etc (12). In order to limit these unwanted effects, stringent donor selection protocols must be adapted (27). Although we already have some data on follow-up for 12-15 months (24), more evidence and larger cohorts with longer follow-up are sorely needed.

Ongoing studies and future perspectives

Currently, there are several ongoing studies in this area, as summarized in table 1.

Several questions still need to be answered regarding FMT in the setting of recurrent HE despite SOC treatment, such as the optimal dose and administration route, long term effects of FMT, the need for antibiotics previously to FMT to facilitate engraftment and the need for a donor selection based on their microbiota profile. Hopefully, ongoing and future trials will answer these questions.

Conclusion

Despite current SOC treatment in overt HE, some patients develop recurrent episodes and need further therapies to control symptoms and improve their quality of life. Thus far, the available evidence for FMT in HE shows promising results as it constitutes a safe, effective and tolerable procedure in these patients. Nevertheless, more evidence is warranted to support these preliminary results.

Acknowledgment

The authors would like to thank Gonalo Torres for the conceptualization and design of the illustration in this article.

Financial support

No funding or writing assistance was provided for this article.

Conflicts of interest

The authors report no conflicts of interest.

Search strategy and selection criteria

References for this Review were identified through searches of PubMed, Cochrane and Clinicaltrials.gov with the search terms “fecal microbiota transplantation”, “FMT” and “hepatic encephalopathy”. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

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