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Research Article

Use of Probiotics as a Prophylaxis for Hepatic Encephalopathy: A Review Article

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Abstract

Hepatic Encephalopathy (HE) is a serious complication of liver cirrhosis and manifests as altered sensorium. It is precipitated by several factors but all these factors result in elevated ammonia levels. Minimal HE (MHE) is a mild form of HE and is not always easy to diagnose. It is mostly recognized by history, physical examination, and neurological tests that assess cognitive function. Altered microbiota in the gut is not uncommon in patients with cirrhosis and often leads to complications. Probiotics have been studied recently for possible use for primary and secondary prophylaxis of HE. Hence, in this review article, we aim to study the role of probiotics in HE prophylaxis. After applying the inclusion and exclusion criteria, we found 8 Randomized Controlled Trials (RCTs). Our results demonstrated that probiotics can be used for possible prophylaxis for MHE. They can be as good as rifaximin and lactulose, common agents occasionally used for prophylaxis. Furthermore, they can also be used for secondary prophylaxis of MHE. Having said that, the authors believe that there is a need to plan RCTs, aiming to use probiotics as a possible treatment for HE.

Keywords: Hepatic Encephalopathy

1. Introduction

Hepatic encephalopathy is a serious complication of liver cirrhosis, involving reversible alteration in consciousness. It is also defined as brain dysfunction caused by liver failure and/or porto-systemic blood shunting. It produces a spectrum of neuro-logical/psychiatric alterations that range from subclinical abnormalities to coma. In the United States, the economic burden of hospitalization for HE amounts to more than $11.9 billion each year, which causes significant increases in patient morbidity and care utilization [1]. Symptoms include personality changes, a depressed level of consciousness, and confusion [2]. According to the West-Haven criteria, the mildest form of HE is minimal HE (MHE). It affects about one-third of patients with liver cirrhosis. Normally, these patients do not have any recognizable clinical symptoms of HE, but they do have mild cognitive and psychomotor deficits that can affect their quality of life [3] and ability to work. Patients with MHE have a higher risk of motor vehicle accidents and are also more susceptible to falls. The prevalence of MHE varies from 30% to 84% in patients with liver cirrhosis and is usually diagnosed with the patient's history, physical/neurological examination findings, along with excluding concomitant neurological disorders, although no standardized criteria have been set so far [2, 3]. HE and MHE usually result from the accumulation of neurotoxic substances in the blood. Several factors can elevate ammonia levels in liver cirrhosis. First and foremost, there is hepatic dysfunction that leads to inadequate ammonia removal from portal venous circulation. Secondly, there is portal hypertension that leads to the portosystemic shunting of blood, which diverts ammonia-containing blood away from the liver to the systemic circulation [4]. Lastly, there is small intestine dysmotility that leads to small intestinal bacterial overgrowth (SIBO). This contributes to increased ammonia production and hence its increased absorption from the gut [5]. Several medications can help lower ammonia levels including L-ornithine-L-aspartate (LOLA), lactulose, rifaximin, etc. Recently the use of probiotics to decrease ammonia levels in the blood is also being considered. Probiotics act by decreasing the urease-producing bacteria in the gut. Studies have been done to assess the efficacy of probiotics in decreasing ammonia levels, evaluating the

role of probiotics for primary and secondary prophylaxis. Treating patients to prevent the development of the first episode of HE is classified as primary prophylaxis while preventing the recurrence of HE in patients who had a previous episode of HE is classified as secondary prophylaxis [6]. Many studies have demonstrated probiotics to be effective in primary and secondary prophylaxis of HE, but there is a lot of heterogeneity. In this review, we not only explore the efficiency of probiotics as a prophylactic drug for MHE and HE but also try to discuss and compare probiotics with other medications commonly prescribed for this purpose.

2. Methods

A search of PubMed was performed to identify relevant research articles. Mesh keywords used included " Hepatic Encephalopathy" AND "Probiotics". The search was restricted to human studies, Randomized Control Trials, and those done in the last 10 years. Articles written in the English language were included. The pediatric population was not included and a filter of >18 years was applied. The exclusion criteria were animal studies.

3. Results

The total number of studies retrieved was 14 initially. After the primary and secondary screening, a total of 8 studies were included in the review. The total number of subjects in our review was 879.

4. Discussion

In this current review, we analyzed data from 8 randomized control trials with a total of 879 subjects. These trials used probiotics in patients with cirrhosis as primary and secondary prophylaxis. The duration of the study in most cases was less than a year with a minimum follow-up period of 1 month [7]. The studies included in our study are summarized in Table 1.

4.1 Importance of gut microbiota especially in liver cirrhosis patients

Recent studies have shown that there is a significant difference between stool microbiota of a healthy person as compared to a person with cirrhosis. In patients with cirrhosis, the number of Autochthonous organisms, which have beneficial roles in the production of bile acids and Short Chain Fatty Acids (SCFAs) (e.g., butyrate), are reduced. On the other hand, pathogenic organisms such as Enterobacteriaceaeare increased, producing endotoxins and lipopolysaccharides, which promote inflammation. This imbalance leads to reduced levels of bile acids and SCFAs and serves to increase intestinal inflammation and permeability, which in turn allows bacterial translocation and systemic inflammation. The administration of probiotics is another technique to modulate the gut microbiota. The purported mechanism of probiotics is to directly increase the population of beneficial bacteria [1]. Table 2 illustrates the different types of probiotics used in our study. Lactobacillus is the most common probiotic that was used in previous RCTs.

4.2 Probiotics use in minimal hepatic encephalopathy

Minimal hepatic encephalopathy (MHE) is a form of HE that is not associated with any grossly evident signs of cognitive dysfunction but cognitive deficits can be demonstrated with neuropsychological testing [2]. Six out of eight studies investigated the role of probiotics in MHE. Xia X et al.studied the role of probiotics in HBV patients [3]. Sharma K et al.compared different medications for possible use for prophylaxis [4]. The remaining 4 studies also made an effort to understand the potential role of probiotics in patients with MHE. All studies except one by Saji S et al. [8] have demonstrated that the use of probiotics does have some potential in reducing ammonia levels and improving overall cognition. The results are demonstrated in Table

3.

4.3 Probiotics use as secondary prophylaxis of hepatic encephalopathy

HE occurs as a complication of advanced liver disease. Many factors can precipitate it and it's very important to prevent it from precipitating as mortality increases with the number and severity of HE episodes [9]. HE not only leads to frequent hospital admissions but also causes poor quality of life and a significant economic burden. No definitive guidelines are available to date for secondary prophylaxis of HE, but rifaximin and lactulose are used for these patients sometimes [10]. Dhiman et al. showed a reduction in the risk of hospitalization, improvement in liver function in terms of CTP (Child-Turcotte-Pugh) and MELD (model for end-stage liver disease) scores, reduction in levels of pro-inflammatory markers, and improvement in HRQOL (Health-related quality of life)with the use of probiotics. Furthermore, these subjects were less likely to develop overt HE [10]. Agrawal A et al. has also demonstrated that probiotics are effective for secondary prophylaxis of HE in patients with hepatic cirrhosis. Hence, probiotics can be used for secondary prophylaxis [11]. Table 4 illustrates these findings.

4.4 Psychometric testing

Psychometric testing is used for the diagnosis of MHE. These tests include Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and PSE-Syndrome-Test. These tests measure multiple domains of brain function.

Author [year]	Date of Publication	Duration of study	Subjects
Xia X, et al [3].	2018	3 months.	67
Dhiman RK, et al [10].	2014	6 months	Total = 130 (probiotics = 66) , placebo (n = 64).
Sharma K, et al [4].	2014	2 months	124 LOLA (n = 31), rifaximin (n = 31), probiotics (n = 32), placebo (n = 30).
Bajaj JS, et al [12].	2014	8 weeks	Total = 30n (14 LGG and 16 placebo)
Lunia MK, et al. [13]	2014	3 months	Total = 160
Ziada DH, et al. [7]	2013	1 month	Total = 90
Agrawal A, et al. [11]	2012	12 months.	Total = 235
Saji S, et al. [8]	2011	--	Total = 43 patients (probiotics =21, placebo group = 22)

Table 1: Illustrates the demographic details of the RCTs included in the review.

Author [year]	Date of Publication	Probiotics used
Xia X, et al. [3]	2018	Clostridium butyricum combined with Bifidobacteriuminfantis
Dhiman RK, et al. [10]	2014	VSL#3, 9 × 10(11) bacteria
Sharma K, et al. [4]	2014	--
Bajaj JS, et al. [12]	2014	Lactobacillus GG (LGG)

Lunia MK, et al. [13]	2014	--
Ziada DH, et al. [7]	2013	Lactobacillus acidophilus)
Agrawal A, et al. [11]	2012	lyophilized bacteria
Saji S, et al. [8]	2011	--

Table 2: Type of probiotic used in each RCT.

Author, Year	Primary Aim of the study	Outcome
Xia X, 2018 [3]	To investigate the role of probiotics in HBV patients.	1) Patients' cognition was improved. 2) The predominant bacteria (Clostridium cluster I and Bifidobacterium) were significantly enriched in the probiotics-treated group, while Enterococcus and Enterobacteriaceae were significantly decreased. 3) Reduction in venous ammonia. 4) Parameters of the intestinal mucosal barrier were improved after probiotic treatment.
Sharma K, 2014 [4]	To determine the prevalence of MHE in patients with liver cirrhosis and to find out the effect of rifaximin, probiotics, and l-ornithine l-aspartate (LOLA).	1) Critical Flicker Frequency (CFF) scores improved. 2) Improvement in psychometric tests.
Bajaj JS, 2014 [12]	To evaluate the safety and tolerability of probiotic Lactobacillus GG (LGG), and its mechanism of action using cognitive, metabolome, micro-biome, and endotoxin analysis.	1) Endotoxemia and TNF-α decreased. 2) Microbiome changed (reduced Enterobacteriaceae and increased ClostridialesIncertaeSedis XIV and Lachnospiraceae relative abundance) with changes in metabolite/microbiome correlations about amino acid, vitamin, and secondary bile acidmetabolism. 3) No change in cognition was found.
Lunia MK, 2014 [13]	To evaluate the efficacy of probiotics for the primary prophylaxis of HE.	1) Significantly reduced levels of arterial ammonia, SIBO, and oro-cecal transit time (OCTT). 2) Increased psychometric hepatic encephalopathy scores. 3) Increased CFF thresholds.
Ziada DH, 2013 Sep [7]	This study aimed to evaluate probiotics as an alternative therapy in MHE.	1) Both probiotics and lactulose therapy can improve blood ammonia and psychometric tests in MHE 2) Both can reduce the risk of developing overt encephalopathy.
Saji S, 2011 [8]	This study aimed to assess the efficacy of probiotics in minimal	Short-term administration of probiotics did not produce any significant improvement when compared with placebo.

	hepatic encephalopathy.	

Table 3: Results of RCTs using probiotics for MHE (Primary prophylaxis).

Author, Year	Primary Aim of the study	Outcome
Dhiman RK, 2014 [10]	Preventing the recurrence of HE (primary outcome) and reducing the number of hospitalizations and severity of liver disease in cirrhotic patients using probiotics	1) Reduction in the development of breakthrough HE. 2) 2) Child-Turcotte-Pugh and MELD scores improved significantly.
Agrawal A, 2012 [11]	To study the effects of lactulose and probiotics for secondary prophylaxis of HE.	Lactulose and probiotics are effective for secondary prophylaxis of HE in patients with cirrhosis.

Table 4: Outcome of studies using probiotics as secondary prophylaxis.

Author [year]	Date of Publication	Method used for screening patients
Xia X, et al. [3]	2018	Number connection test (NCT) and digit symbol test (DST).
Dhiman RK, et al. [10]	2014	--
Sharma K, et al. [4]	2014	Three neuropsychometric tests (NPTs) and critical flicker frequency (CFF) test.
Bajaj JS, et al. [12]	2014	Serum, urine, and stool samples were collected.
Lunia MK, et al. [13]	2014	Psychometric analyses, critical flicker fusion (CFF) threshold assessments, glucose hydrogen breath tests to identify small intestinal bacterial overgrowth (SIBO), and lactulose hydrogen breath tests to measure oro-cecal transit time (OCTT).
Ziada DH, et al. [7]	2013	Tested for gut microecology, fasting blood ammonia, liver functions, and magnetic resonance spectroscopy (MRS) examination to study brain metabolites, mainly choline (Cho), myo-inositol (mI), glutamine + glutamate (Glx), and creatinine (Cre).
Agrawal A, et al. [11]	2012	Assessed by psychometry (number connection test (NCT-A, B), figure connection test if illiterate (FCT-A, B), digit symbol test (DST), and block design test (BDT)), critical flicker frequency (CFF) test, and arterial ammonia at inclusion.
Saji S, et al. [8]	2011	Diagnosed by number connection test (NCT) and evoked responses were recruited for the study.

Table 5: Illustrates different tests used to screen the patients initially and at the end of the study.

5. Conclusion

In summary, the present data have important implications for MHE treatment with probiotics. Probiotics can modulate the intestinal microbiota, which plays a vital role in re-establishing the intestinal mucosal barrier function. Restoration of the intestinal barrier contributes to a decrease in the blood ammonia level. The present study also indicates that probiotics can be used as an effective therapy for HE in clinical practice.

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