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Benefit of probiotics in preventing hepatic encephalopathy among patients with liver cirrhosis: an evidence-based case report

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Background: Hepatic encephalopathy (HE) is a serious complication in patients with liver cirrhosis. Its pathogenesis involved the mechanism of HE including endotoxins, ammonia production and other neurotoxins by gut microflora. Probiotic exert potential benefit for gastrointestinal microflora. The use of probiotics may provide substantial benefit for the treatment of HE.

Objective: This report aimed to evaluate the benefit of probiotics in preventing HE among liver cirrhosis patients.

Methods: Literature searching with keywords of 'liver cirrhosis', 'probiotics', 'hepatic encephalopathy' along with its synonyms and related terms was implemented in Pubmed. Additional hand-search was implemented to obtain the relevant articles.

Result: Three meta-analyses showed that probiotics are effective to prevent HE development. All meta-analyses obtained similar results, in which the odds ratio (OR) obtained was ranging from 0.22 to 0.42. One randomized controlled trial (RCT) by Dhiman et al showed that probiotics treatment reduces the relative risk of overt HE by 33% compared to placebo.

Conclusion: Probiotics administration exert potential to prevent the development of HE in the liver cirrhotic patients. The patient may benefit with the given of probiotics.

Keywords: *Hepatic encephalopathy, cirrhosis, probiotics, prevention.*

INTRODUCTION

Hepatic encephalopathy (HE) served as one of serious complication in patients with liver cirrhosis. It impacts on reversible alteration in consciousness. Another definition is a brain dysfunction due to liver failure or porto-systemic blood shunting. Its clinical manifestation including alteration in neurological or psychiatric component. It could range from mild alteration in level of consciousness to coma.[1]

Overt HE estimated to occur in approximately 30% to 45% of cirrhosis patients.[2] A study by Bustamante et al[3] found that the survival probability at 1 and 3 years of monitoring of the patient after the first episode of HE was 42% and 23%, respectively. The increase in frequency, along with its severity predict an increased risk of death.[4] As for health burden for HE, the economic burden of hospitalization reached up to more than $11.9 billion each year in the United States. It leads to significant increases in morbidity and care utilization.[5]

The pathogenesis of HE has been studied for long time. Factors involving in the mechanism of HE including endotoxins, ammonia production and other neurotoxins by gut microflora. It has been known that there are alteration in fecal microbiota of liver cirrhosis patients. It served as indirect evidence that the pathogenic bacteria increase and trigger inflammatory process, resulting in production of cytokines and leads to impairment in cognitive function.[6,7] Another study also found that small intestinal bacterial overgrowth (SIBO) was higher in liver cirrhosis patients with minimal HE (MHE) compared to patients without MHE (38.6 vs. 8.9 %, respectively).[8]

Probiotic, along with prebiotic and synbiotics exert potential benefit for gastrointestinal microflora. They also provide substantial role in maintaining normal healthy state. The use of probiotics may provide substantial benefit for the treatment of HE. Probiotics may decrease the amount of pathogenic bacteria, thus improving endotoxemia, HE and liver function.[7] Various studies have extensively evaluating the use of probiotics for MHE and overt HE. A study by Mouli et al about the efficacy of probiotics found that the improvement rate in MHE and decrease of ammonia similar when compared to lactulose after two months of treatment.[9]

Hepatic encephalopathy is associated with mortality and poor quality of life in cirrhotic patients. Preventing development of HE is an important aspect of cirrhosis treatment. This article reported a case of patient with HE and we presented a critical appraisal of the role of probiotics to prevent development of HE compared to placebo.

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CASE ILLUSTRATION

A 63-year-old woman with history of hepatocellular carcinoma and liver cirrhosis (Child-Turcotte-Pugh Class C) presented to emergency department with hematemesis. She was delirious (GCS E3V4M6), hypotensive (blood pressure 88/50 mmHg, heart rate 80 bpm), and anemic (Hb 5.5 mg/dL). She was diagnosed with HE and probable rupture of esophageal varices. After initial fluid resuscitation, she received blood transfusions, continuous omeprazole infusion, antibiotics, probiotics and lactulose. Her condition subsequently improved and she was discharged after six days.

The above case raises a clinical question regarding the use of probiotics in liver cirrhosis patients. A question arises whether probiotics prevent hepatic encephalopathy among patients with liver cirrhosis.

METHODS

The search strategy implemented in this report used several related keywords according to patient, intervention, control and outcome (PICO) method (Table 1) and search engine in Pubmed. Additional hand-search was implemented to obtain the relevant articles of therapeutic studies using probiotics to prevent HE. The keywords including 'liver cirrhosis', 'probiotics', 'hepatic encephalopathy' along with its synonyms and related terms.

Initial search on October 10th, 2020 yielded 39 studies. A total of 38 studies obtained from Pubmed and one article from hand-searching. The title and abstract screening obtained six related articles and further evaluation for duplications excluded three additional articles. In the final phase, three meta-analysis studies were appraised for their validity, results, and applicability (Figure 1).

RESULTS

Three meta-analysis showed that probiotics are effective to prevent HE development (Table 1).[10-12] A meta-analysis by Xu et al[10] had appropriate inclusion criteria with low risk of bias for the quality of included studies. However, meta-analysis by Cao et al[11] and Dhiman et al[12] were high risk of bias based on the assessment for its quality of included studies. All meta-analyses obtained similar results, in which the OR obtained was ranging from 0.22 to 0.42. All studies were applicable to be implemented (Table 2). One randomized controlled trial (RCT) by Dhiman et al[13] in 2014 showed that probiotics treatment reduces the relative risk of overt HE by 33% compared to placebo. Additionally, probiotics are well-tolerated for long term use with minimal adverse effects.

DISCUSSION

Existing studies showed that the stool microbiota of healthy person is significantly difference compared to patients with liver cirrhosis. The imbalance of organisms which responsible in bile acids and short chain fatty acids (SCFAs) production occurred in liver cirrhosis patients. There is a decrease in Autochthonous organisms, responsible for the production of bile acids and SCFAs, while Enterobacteriaceaeare, pathogenic organisms, is increasing in number. Enterobacteriaceaeare promote the inflammation process by promote endotoxins and lipopolysaccharides. The resulting effects of this imbalance are the increase in intestinal permeability and inflammation. This may promote the translocation of bacteria and systemic inflammation.[1]

Probiotics able to modify gut flora when ingested in adequate amounts. Probiotics may alter these imbalance by reduce the amount of pathogenic bacteria and alter

Table 1. PICO question

Patient	Intervention	Control	Outcome
Patients with liver cirrhosis	Probiotics	Placebo	Hepatic encephalopathy

Table 2. Critical appraisal of three articles evaluating the benefit of probiotics in preventing hepatic encephalopathy among patients with liver cirrhosis.

Meta-Analysis	n	Validity			Results		Applicability
		Unlikely to miss relevant studies	Appropriate inclusion criteria	Quality of included studies	Similar results	Weighted OR (95% CI)	
Xu, 2014[10]	394	No	Yes	Low risk of bias	Yes	OR 0.42 (0.26-0.70)	Yes
Cao, 2018[11]	191	No	Yes	High risk of bias	Yes	OR 0.22 (0.07-0.67)	Yes
Dhiman, 2020[12]	252	Yes	Yes	High risk of bias	Yes	OR 0.24 (0.09-0.62)	Yes

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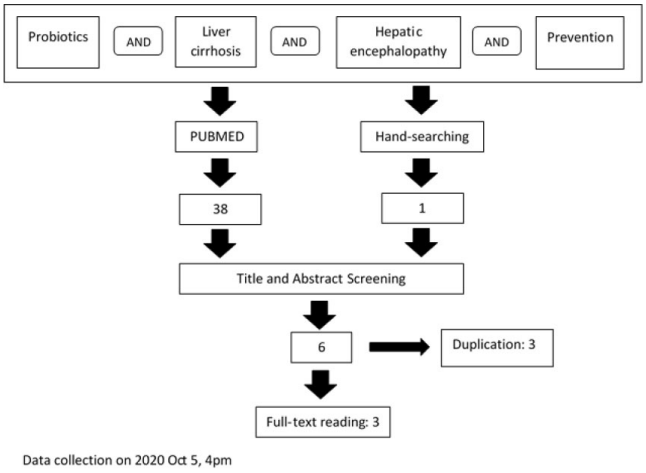

Figure 1. Searching strategy flowchart.

endotoxemia, liver functions and HE.[7] These factors leads to improvement of gut dysbiosis. There are several proposed mechanisms of action responsible for this effect. By suppress the activity of bacterial urease, gut microbiota lower the levels of ammonia in the portal blood. They may also decrease intestinal permeability. The second mechanism related to the effect of decreasing endotoxemia. The third mechanism including decrease in the uptake of toxins, e.g., mercaptans, oxindoles, indoles and phenols.[14,15] This benefits for liver cirrhosis patients with HE or MHE, in which inflammatory process possess significant involvement in its pathogenesis.[16]

Hepatic encephalopathy served as complication of advanced liver disease. Several important factors precipitate its occurrence. The prevention of HE is mandatory since its occurrence and the severity associated with the likelihood of mortality for liver cirrhotic patients.[17] This complication lead to worse quality of life and increase in the rate of hospitalization. It resulting in significant economic burden. To date, no guidelines exist regarding the secondary prophylaxis of HE. However, rifaximin and lactulose are used in this type of population.[18]

After a thorough searching, three articles were finally critically appraised. All three studies, were meta-analysis, along with one article of RCTs. All meta-analysis have relatively good validity (a study by Dhiman et al has potential to miss relevant articles and two studies have high risk of bias). All meta-analyses have similar results and good applicability. Furthermore, all studies matched our clinical question.

A study by Xu et al in 2014 investigating the role of probiotics on liver cirrhotic patients with hepatic encephalopathy. In their study, they obtained six randomized controlled trials with a total of 496 patients with liver cirrhotic. The result showed that probiotic therapy significantly reduced the development of overt hepatic encephalopathy with OR 0.42. In their study, the total patients who received probiotics for the analysis of overt HE was 207 patients, while control was 187 patients. However, probiotics did not affect mortality, levels of serum ammonia and constipation.[10]

Another meta-analysis study by Cao et al in 2018 also obtained similar results. In their study, a total of 14 RCTs were included. The results obtained showed that probiotics were more likely to prevent overt HE progression at week 4, with OR of 0.22. However, the result at weeks 12 showed no significant difference to prevent over HE. The total patients involved for the analysis of this outcome was 96 patients for probiotics and 95 patients for placebo or no intervention group.[11]

One study by Dhiman et al in 2020 found the reduction risk of development to overt HE with the use of probiotics, when compared to placebo or no intervention with OR of 0.24. In their study, this outcome involved 5 RCTs, analyzing studies which compared probiotics with placebo or no treatment. The use of L-ornithine-L-aspartate (LOLA) also exerts similar results with OR of 0.19, but not for rifaximin.[12]

All studies have great applicability in the clinical setting. The overall result showed that the use of probiotic benefits to prevent the development of HE in liver cirrhotic patients. However, the current report also subjected to some limitations. There is no head-to-head comparison between probiotics and other modalities in regards to prevention of HE in liver cirrhotic patients. Furthermore, the duration of probiotics administration still become a major issue in the clinical use of this treatment. Furthermore, since one study showed no effects of probiotic treatment to prevent HE in weeks 12,[11] the study for long term efficacy of probiotic also warranted for more inn-depth evaluation.

CONCLUSION

The administration of probiotics is useful to prevent hepatic encephalopathy in liver cirrhotic patients. In our case, the patient described may benefit from probiotics treatment.

CONFLICT OF INTEREST

The authors report no conflicts of interest regarding this study.

ETHICS CONSIDERATION

This case report has obtained informed consent from the patient as well as the following COPE for publication ethics guidelines.

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AUTHOR CONTRIBUTIONS

AAYP responsible for the treating the patient, evaluating and monitoring of the patient, data acquisition, data analysis, and reporting the study results through publication.

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