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ORIGINAL ARTICLE

Role of Probiotics in Secondary Prophylaxis of Hepatic Encephalopathy

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ABSTRACT

Aim: To determine the role of probiotics in combination with standard therapy in secondary prophylaxis of hepatic encephalopathy.
Methods: This Randomized Controlled Trial was carried out in the Medical Wards of King Edward Medical University/Mayo Hospital, Lahore from 15th October, 2018 to 14th January, 2020. 166 patients selected via simple random sampling technique were divided into two groups. Group A received Lactulose whereas Group B received Lactulose plus Probiotic. A three months follow up for each patient was done. Absence of hepatic encephalopathy at the end of treatment was considered Effective treatment response. Primary end point was completion of three months or development of hepatic encephalopathy. Patients' responses were noted on a pre-designed proforma. Data analysis was done using SPSS version 23.0.
Results: Out of a total of 166 patients comprising 83 males and 83 females, mean age of the patients was 54.11±7.76 years. A statistically significant difference was found between the study groups inserum ammonia levels(p-value=<0.001). At 3rd month follow up 79(47.59%) patients had no episode of hepatic encephalopathy as assessed on West Haven grading (grade 0) followed by hepatic encephalopathy noted in 56(33.73%) patients; 25(15.06%)ingrade 3, 22(13.25%)ingrade 4 and 9(5.42%)in grade 2 respectively. p-value between the study groups and end result of the patients demonstrated statistically significant difference(p-value=0.028)
Practical Implication: Overt hepaticencephalopathy is a common and frequent complication in patients with decompensated chronic liver disease. Various treatment modalities have proven beneficial. In this study we have shown the adjuvant role of probiotics with the standard lactulose therapy in remission and secondary prophylaxis of overt hepatic encephalopathy.
Conclusion: Probiotics in conjunction with conventional lactulose therapy is more effective than standard lactulose therapy alone in remission and maintenance of secondary prophylaxis of overt hepatic encephalopathy.
Keywords: Hepatic Encephalopathy, Secondary prophylaxis, Standard therapy, Probiotic

INTRODUCTION

Cirrhosis is the 11th most common cause of death globally[1]. Hepatic Encephalopathy (HE), a reversible illness is defined as impaired brain function accredited to liver insufficiency and/or portosystemic blood shunting. It encircles a spectrum of neuropsychiatric and motor abnormalities varying from mild cognitive impairmenttomarked disorientation, confusion, coma, and even death as one of its sequelae[2]. The incidence of HE is 11.6 per 100 person years that increases to 40% by 5 years[3]. About 10–14% of cirrhotic patients havehepatic encephalopathy when diagnosed and 16–21% have decompensated cirrhosis.[4] Prevalence of MHE is variable ranging from 20-80%. Within five years of cirrhosis, there is a 5–25% chance of experiencing the first episode of overt hepatic encephalopathy[5].

Hepatic encephalopathy is subcategorized into three main types based on pathophysiology. Type A attributed to acute liver failure, Type B associated with portosystemic bypass/shunting and Type C associated with liver cirrhosis and portal hypertension .According to severity of manifestation, hepatic encephalopathy is classified as minimal hepatic encephalopathy (MHE), covert and overt encephalopathy, which is further graded on West Haven grading. Covert HE, a sub-type of type C HE, is found in 80% of cirrhotic patients and is diagnosed by well-established psychometric tests. It includes MHE and grade 1 of Overt HE (OHE)[6].

Blood ammonia is the best characterized neurotoxin and main culprit linked to pathogenesis of hepatic encephalopathy. Furthermore, systemic and neuroinflammation, oxidative stress and cellular senescence are also implicated[7]. Neurological impairment is also caused by impaired brain glymphatic flow, deranged blood brain barrier function and permeability and distorted composition of the cerebrospinal fluid[8].The gastrointestinal (GI) tract is the primary source of ammonia produced as the output of protein absorption, deamination of amino acids and bacterial urease activity[4].In patients of liver disease, there is alteration in metabolism of ammonia[9,10].

Probiotics are defined by the World Health Organization(WHO) and International Scientific Association for Probiotics and Prebiotics (ISAPP) as"live microorganisms which when administered in adequate amounts confer a health benefit to the host"[11,12]. They are living non-pathogenic microorganisms that work on gut flora and decrease ammonia production as well as absorption through reduction of pH, modulation of GI immune response through alteration of inflammatory cytokines and downregulation ofproinflammatory cascades thereby contributing to an overall improvement in Child Turcotte Pugh (CTP) score, reduction of endotoxinlevels in cirrhotic patients and increased hepatic clearance of ammonia[13].

Various studies have highlighted the role of probiotics when given alone or when combined with standard therapy for the management of MHE and OHE but with a wide range of discordance.Xia et al established a significant role of probiotics in MHE patients with HBV cirrhosis and showed an additional role of probiotics in reducing venous ammonia level and improving cognition[14].

In a study administered by Rocco et al and Pratap Mouli et al, probiotics were found non-inferior to lactulose in ameliorating MHE and averting HE in cirrhotic patients[15,16].

However, Marlicz et al through his study demonstrated no significant difference in the incidence and grade of HE with probiotic supplementation[17].

Keeping in view the mortality and morbidity attributed to HE and the change of emphasis from treating HE to preventing it, this study was planned with the aim to draw inference from the role of probiotics in our cirrhotic population by carrying out a proper patient selection with well-defined clinical end objectives and sufficient follow-up.

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METHODS

This Randomized Controlled Trial was carried out in the Medical Wards of King Edward Medical University/ Mayo Hospital, Lahore from 15th October, 2018 to 14th January, 2020 after getting permission from KEMU Ethical Committee.

Sample Size: Sample size of 166 patients (83 in each group) was computedtaking level of significance as 5%, power of test as 90% and expected percentage of overt hepatic encephalopathy with probiotics and control group as 34.4% and 56.9% respectively.

Sampling Technique: Simple random sampling technique was employed in patient selection.

Inclusion Criteria: Patients of either sex falling in the age group of 18-75 years and diagnosed cases of liver cirrhosis irrespective of etiology and in any grade of hepatic encephalopathy based on West Haven Criteria were included in the study.

Exclusion Criteria: Patients with significant co-morbid illness like heart, respiratory or renal disease,hepatocellular carcinoma and history of transjugular intrahepatic portosystemic shunting, recent alcohol intake and use of antibiotics in the last 6 weeks, patients taking psychotropic drugs like antidepressant, narcotics, sedatives and having central nervous system disorders like Alzheimer's disease, Parkinson's disease etc were barred from the study.

Data Collection Procedure: After getting approved from the Advanced Study Research Board (ASRB) of King Edward Medical University, 166 patients complying with the selection criteria were enrolled. Informed written consent was taken from the patients or their first degree relatives. Demographic data was obtained. Baseline investigations included CBC, LFTs,Prothrombin time(PT), serum creatinine, Ultrasound abdomen and arterial ammonia levels. Patients were divided by Lottery method into Group A that received Lactulose(upto 180ml per day) and Group B that received Lactulose and Probiotic [Cap.Ecotec 180mg,1 billion CFU (Lactoacidic, Bifidobectrium, S.thermophilus, Lactobulgarius)] twice daily. Both these groups received treatment for three months and were followed up on a monthly basis in the OPD and were assessed by Psychometric testing (Number connection test, serial dotting, line tracing and digital symbol test). Patients who developed hepatic encephalopathy during follow up period were considered as treatment failure. The absence of hepatic encephalopathy throughout the study period was considered as effective treatment response. Primary end point was the completion of three months or development of hepatic encephalopathy.

Data Analysis: Data was analyzed using SPSS version 23.0. Quantitative data like age, grade of hepatic encephalopathy were addressed as Mean±SD. Qualitative variables like gender, presence or absence of hepatic encephalopathy were presented as frequencies and percentages. Chi square test was applied forcomparing both groups. P-value less than 0.05 was taken as significant.

RESULTS

Out of 166 patients, mean age of the patients was 54.11±7.76 years (55.84±7.63 years in Group A and 52.37±7.54 years in Group B). Male to female ratio was equal however Group A had a female preponderance i.e., 46 (55.4%). Comparison of the clinical variables is given in Table 1. Comparison of ascites between the two groups showed mild ascites in 29(34.9%)patients in group A and in 38(45.8%) in group B whereas moderate ascites was found in 29(34.9%) in Group A and in 31(37.3%) in group B. 25(30.1%)patients in group A and 14(16.9%) in group B had no ascites at presentation. p value for ascites was calculated to be 0.112. Psychometric tests undertaken by the patients in both groups at the time of presentation yielded normal results. Comparison of different psychometric tests at the end of 2nd and 3rd months is given in table 2 and 3.

Table 1: Comparison of clinical variables between study groups**Clinical Variables**

	Study Groups		**p-value**
	A	**B**	
Bilirubin	1.32±0.63	1.15±0.55	0.068
ALB	2.84±0.34	2.8060±0.34	0.431
Creatinine	0.69±0.14	0.69±0.14	0.956
Liver size	13.33±1.17	13.52±1.06	0.277
Spleen Size	12.13±1.21	12.16±1.20	0.893
Prothrombin Time	4.9±0.72	5.1±0.85	0.352
Baseline Ammonia	58.95±6.35	59.49±5.93	0.582
Ammonia at follow up	83.45±38.15	64.19±20.015	<0.001

Table 2: Comparison of different Psychometric test findings at 2nd month

2nd Month follow up	**Study Groups**		**Total**	**P value**
	A	**B**		
Number connection test				
Abnormal	11(13.3%)	6(7.2%)	17(10.2%)	0.386
Normal	69(83.1%)	75(90.4%)	144(86.7%)	
NA	3(3.6%)	2(2.4%)	5(3.0%)	
Serial dotting test				
Abnormal	11(13.3%)	6(7.2%)	17(10.2%)	0.386
Normal	69(83.1%)	75(90.4%)	144(86.7%)	
NA	3(3.6%)	2(2.4%)	5(3.0%)	
Line tracing test				
Abnormal	11(13.3%)	6(7.2%)	17(10.2%)	0.386
Normal	69(83.1%)	75(90.4%)	144(86.7%)	
NA	3(3.6%)	2(2.4%)	5(3.0%)	
Digital symbol test				
Abnormal	11(13.3%)	6(7.2%)	17(10.2%)	0.386
Normal	69(83.1%)	75(90.4%)	144(86.7%)	
NA	3(3.6%)	2(2.4%)	5(3.0%)	

Table 3: Comparison of different Psychometric test findings at 3rd month

3rd Month follow up	**Study Groups**		**Total**	**P value**
	A	**B**		
Number connection test				
Abnormal	32(38.6%)	24(28.9%)	56(33.7%)	0.025
Normal	31(37.3%)	48(57.8%)	79(47.6%)	
NA	20(24.1%)	11(13.3%)	31(18.7%)	
Serial dotting test				
Abnormal	32(38.6%)	24(28.9%)	56(33.7%)	0.025
Normal	31(37.3%)	48(57.8%)	79(47.6%)	
NA	20(24.1%)	11(13.3%)	31(18.7%)	
Line tracing test				
Abnormal	32(38.6%)	24(28.9%)	56(33.7%)	0.025
Normal	31(37.3%)	48(57.8%)	79(47.6%)	
NA	20(24.1%)	11(13.3%)	31(18.7%)	
Digital symbol test				
Abnormal	32(38.6%)	24(28.9%)	56(33.7%)	0.025
Normal	31(37.3%)	48(57.8%)	79(47.6%)	
NA	20(24.1%)	11(13.3%)	31(18.7%)	

Figure 1 and 2 shows the distribution of hepatic encephalopathy according to West Haven Grading at the end of 2nd and 3rd month of follow-up.

Fig.1: Distribution of West Haven grading at 2nd month

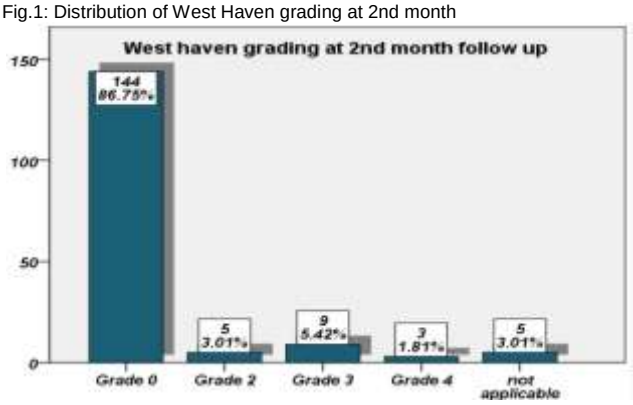
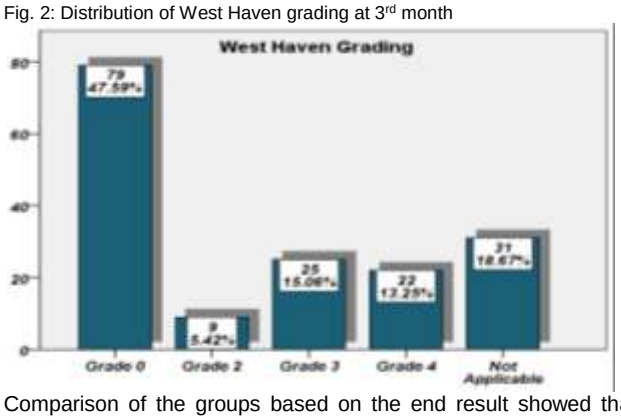


Fig. 2: Distribution of West Haven grading at 3rd month



Comparison of the groups based on the end result showed that 31(37.3%) patients in group A and 48 (57.8%) patients in group B completed the study. 43(51.8%) patients from group A and 30(36.1%) patients in group B had treatment failure. Only 9(10.8%) in group A and 5(6%) patients in group B were lost to follow-up (p value 0.028).

DISCUSSION

In cirrhotic patients, there is a very high occurrence of HE accounting to approximately 50-70% and is linked to bad prognosis with an estimated one year survival rate to be 42% and three year survival rate to be 23%. Several studies have demonstrated the role of probiotics with lactulose or placebo in treating hepatic encephalopathy. Philip Hendy and Nik Ding showed a significant reduction in HE in patients treated with probiotics (34.8% in the probiotic group versus 51.6% in the placebo group, p=0.12)[18]. The grade of HE was noticeably lower in the probiotic group (p=0.01) as well the number of hospitalizations (p=0.034).

Sharma et al. used probiotics for treating patients with MHE showed substantial results in terms of better psychometric profile, blood ammonia levels and abnormal EEG results[19]. Agrawal A et al in their study failed to show a significant role of probiotics and lactulose in treating HE (p= 0.349)[20] .

Another study by Radha K. Dhiman et al showed lower hospitalization rates for HE (19.7% vs 42.2%) and cirrhosis complications (24.2%) in the probiotic versus the placebo group (45.3%). Daily use of probiotics throughout a six-month period dramatically decreased the chance of HE hospitalizations[21].

Dalal et al conducted a meta-analysis of 21 intervention trials involving 1,420 patients anddemonstrated that addition of probiotic was associated with decreased untoward events when compared with either a placebo or no treatment.reduced adverse events attributed to HE and also lowered plasma ammonia concentration thereby improving quality of life[22].

Cao et al concluded that there is a reduction in serum ammonia and endotoxin levels as a result of probiotic use that not only improves MHE but also prevents OHE in patients with liver cirrhosis. They also showed equal efficacy of probiotics and lactulose in MHE patients[23].

A meta-analysis by Dhiman et al involving 1,563 patients from 25 different clinical trialscompared probiotics with placebo or no treatment and demonstrated complete reversion of MHE and prevention of OHE[24].

Khoruts et al addressed the difficulty in comparing data suggesting probiotic use in HE owing to the availability of various strains of probiotics and their modes of delivery, diversity of study designs and their reported outcome[25].

The results of this study correspond to the results of the above mentioned studies. Moreover it also substantiates the role of serum ammonia levels at presentation and at least two impaired psychometric tests in strongly predicting subsequent occurrence of HE. These are simple bedside/ OPD tests and their widespread clinical application for evaluation of HE needs to be emphasized.

CONCLUSION

This study concluded an effective role of probiotics when given with standard treatment (lactulose)in remission and maintenance of secondary prophylaxis of overt hepatic encephalopathy when compared with standard therapy alone.

Conflict of interest: Nil

REFERENCES

1. Asrani SK, Devarbhav H, Eaton J, Kamath PS. Burden of liver diseases in the world. J Hepatol. 2019 Jan;70(1):151-171. doi: 10.1016/j.jhep.2018.09.014. Epub 2018 Sep 26.
2. Weissenborn, Karin. “Hepatic Encephalopathy: Definition, Clinical Grading and Diagnostic Principles.” *Drugs* 79 (2018): 5 - 9.
3. Tapper EB, Henderson JB, Parikh ND, Ioannou GN, Lok AS. Incidence of and risk factore of hepatic encephalopathy in a population-based cohort of Americans with cirrhosis. HepatolCommun, 3(2019),1510-1519
4. Rose CF, Amodio P, Bajaj JS, et al. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. Journal of Hepatology. 2020 Dec;73(6):1526-1547. DOI: 10.1016/j.jhep.2020.07.013. PMID: 33097308.
5. Allampati S, Duarte-Rojo A, Thacker LR, Patidar KR, White MB, Klair JS, et al. Diagnosis of minimal hepatic encephalopathy using StroopEncephalApp: a multicenter US-based, norm-based study. Am J Gastroenterol 2016;111:78–86.
6. Butterworth RF. Hepatic Encephalopathy in Cirrhosis: Pathology and Pathophysiology. Drugs. 2019 Feb;79(Suppl 1):17-21. doi: 10.1007/s40265-018-1017-0. PMID: 30706423; PMCID: PMC6416236.
7. Görg B, Karababa A, Häussinger D. Hepatic encephalopathy and astrocyte senescence. J ClinExpHepatol 2018;8:294–300.
8. Hadjihambi A, Harrison IF, Costas-Rodríguez M, Vanhaecke F, Arias N, Gallego-Durán R, et al. Impaired brain glymphatic flow in experimental hepatic encephalopathy. J Hepatol 2019;70:40–49.
9. Wright G, Noiret L, Damink SWMO, Jalan R. Interorgan ammonia metabolism in liver failure: the basis of current and future therapies. Liver Int 2011;31:163–175.
10. Dasarathy S, Mookerjee RP, Rackayova V, RangrooThrane V, Vairappan B, Ott P, et al. Ammonia toxicity: from head to toe? Metab Brain Dis 2017;32:529–538.
11. FAO/WHO (2009). *Evaluation of Health and Nutritional Properties of Probiotics in Food Including Powder Milk with Live Acid Bacteria*.Available at https://www.fao.org/3/a0512e/a0512e.pdf . Córdoba, Argentina: Report of a Joint FAO/WHO Expert Consultation.
12. Hill, C., Guarner, F., Reid, G. *et al.* The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev GastroenterolHepatol* 11, 506–514 (2014). https://doi.org/10.1038/nrgastro.2014.66
13. Lunia M. K., Sharma B. C., Sharma P., Sachdeva S., Srivastava S. (2014). Probiotics Prevent Hepatic Encephalopathy in Patients with Cirrhosis: A Randomized Controlled Trial. *Clin.Gastroenterol.Hepatol.* 12, 1003–1008. 10.1016/j.cgh.2013.11.006
14. Xia X., Chen J., Xia J., Wang B., Liu H., Yang L., et al. (2018). Role of Probiotics in the Treatment of Minimal Hepatic Encephalopathy in Patients with HBV-Induced Liver Cirrhosis. *J. Int. Med. Res.* 46, 3596–3604. 10.1177/0300060518776064
15. Rocco A, Sgamato C, Compare D, Coccoli P, Nardone OM, Nardone G. Gut Microbes and Hepatic Encephalopathy: From the Old Concepts to New Perspectives. Front Cell Dev Biol. 2021 Nov 26;9:748253. doi: 10.3389/fcell.2021.748253. PMID: 34900994; PMCID: PMC8662376.
16. PratapMouli V., Benjamin J., Bhushan Singh M., Mani K., Garg S. K., Saraya A., et al. (2015). Effect of Probiotic VSL#3 in the Treatment of Minimal Hepatic Encephalopathy: A Non-inferiority Randomized Controlled Trial. *Hepatol. Res.* 45, 880–889. 10.1111/hepr.12429
17. Marlicz W., Wunsch E., Mydlowska M., Milkiewicz M et al. (2016). The Effect of Short Term Treatment with Probiotic VSL#3 on Various Clinical and Biochemical Parameters in Patients with Liver Cirrhosis. *J. Physiol. Pharmacol.* 67, 867–877
18. Hendy P, Ding N. Probiotics for secondary prevention of hepatic encephalopathy. British Medical Journal Publishing Group; 2015.
19. Sharma P, Sharma BC, Puri V. An open-label randomized controlled trial of lactulose and probiotics in the treatment of minimal hepatic encephalopathy. European journal of gastroenterology & hepatology 2008; 20(6): 506-11.
20. Agrawal A, Sharma BC, Sharma P, Sarin SK. Secondary prophylaxis of hepatic encephalopathy in cirrhosis: an open-label, randomized controlled trial of lactulose, probiotics, and no therapy. The American journal of gastroenterology 2012;107(7):1043.
21. Dhiman RK, Rana B, Agrawal S, Garg A, Chopra M, Thumburu KK, et al. Probiotic VSL# 3 reduces liver disease severity and hospitalization in patients with cirrhosis: a randomized, controlled trial. Gastroenterology 2014;147(6):1327-37. e3.
22. Dalal R., Mcgee R. G., Riordan S. M., Webster A. C. (20172017). Probiotics for People with Hepatic Encephalopathy. *Cochrane Database Syst. Rev.* 2021, CD008716. 10.1002/14651858.CD008716.pub3
23. Cao Q., Yu C.-B., Yang S.-G., Cao H.-C., Chen P., Deng M., et al. (2018). Effect of Probiotic Treatment on Cirrhotic Patients with Minimal Hepatic Encephalopathy: A Meta-Analysis. *Hepatobiliary Pancreat. Dis. Int.* 17, 9–16. 10.1016/j.hbpd.2018.01.005
24. Dhiman R. K., Thumburu K. K., Verma N., Chopra M., Rathi S., Dutta U., et al. (2020). Comparative Efficacy of Treatment Options for Minimal Hepatic Encephalopathy: A Systematic Review and Network Meta-Analysis. *Clin.Gastroenterol. Hepatol.* 8, 800–812, e25. 10.1016/j.cgh.2019.08.047
25. Khoruts A., Hoffmann D. E., Britton R. A. (2020). Probiotics: Promise, Evidence, and Hope. *Gastroenterology* 159, 409–413. 10.1053/j.gastro.2020.05.058