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Research Article

Role of Probiotics in Secondary Prophylaxis of Hepatic Encephalopathy

Muhammad Farooq Hanif *[1], Abdul Rehman [2], Raja Omer Fiaz [3], Maria [4], Memoona Hanif [5], Khalid Mehmud Khan [6]

***Correspondence to:** Muhammad Farooq Hanif,.

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Abstract

Background & Aim: *Cirrhosis is a condition in which long-term damage to the liver impairs its functioning. Hepatic encephalopathy (HE) is a syndrome observed in patients with cirrhosis which results in the accumulation of ammonia in the body which is toxic to the brain and harms neurons and astrocytes. Many of the symptoms of hepatic encephalopathy are reversible when promptly identified and treated. Probiotics are live microorganisms, which when administered in adequate amounts may confer a health benefit to the host. We conducted this study aiming to find out better treatment bundles that can long-term prevent HE.*

Material & Methods: *Selected patients were randomized to group A (Lactulose) and group B (Lactulose + Probiotics). Each patient was followed for one year for hepatic encephalopathy recurrence.*

Results: *A total of 166 patients were made a part of this study and 152 completed the study. The mean age was 55.84±7.82 and 52.37±6.95 in groups A and B respectively. The majority of patients were of child class B (75.90%). Overall encephalopathy occurred in 51.80% and 36.14% of patients in groups A and B respectively (p =0.02). Encephalopathy was more common among relatively older females and patients with child class C. Abdominal bloating, distaste, and diarrhea were the common side effects in both groups with no significant difference in the side effect profile. Patients were compliant with the treatment in both groups.*

Conclusion: *Our study of cirrhotic patients who received probiotics in combination with lactulose showed significant long-term secondary prevention of hepatic encephalopathy, compared to those who received only lactulose.*

Keywords: *Hepatic encephalopathy, Cirrhosis, Effectiveness, Lactulose, Probiotics.*

Introduction

Cirrhosis makes itself the 12th paramount cause of death worldwide **[**1**]**. One of the major complications that arise in a liver cirrhosis patient is Hepatic Encephalopathy (HE), which is a reversible disorder comprising of broad spectrum neuro-psychiatric and motor disturbances including non-cognizant neuro-sensory state, coma & even death **[**2**]**. The prevalence of HE at the time of diagnosis of cirrhosis ranges from 10-14% predominantly, with decompensated cirrhotics contributing 16-21% and 30-40% prevalence in people with cirrhosis at some time during their clinical course **[**3**]**. The risk for the first bout of HE is 5-25% in a span of the first 5 years after cirrhosis **[**4**]**. Ammonia is the key factor in the induction of glutamate toxicity leading to augmentation of the GABA receptor system in the brain resulting in HE. High levels of ammonia are found in 90% of patients with HE. Enterocytes are responsible for its production from glutamine and colonic bacterial catabolism of nitrogenous sources results in augmentation of ammonia levels. Ammonia makes its way into the circulation and affects brain function. Astrocytes make up 1/3rd of the cerebral cortex and are primarily affected. They are involved in blood-brain barrier function and regulation of the release of neurotransmitters **[**5**]**. Lactulose, a non-absorbable disaccharide remains the treatment of choice in HE whose efficiency is proven for both primary and secondary prophylaxis. Lactulose, commonly used as a safe drug in HE treatment, decreases the passive non-ionic diffusion of ammonia and its systemic concentration **[**2**]**. Additionally, rifaximin is also in use along with lactulose for the treatment of secondary prophylaxis of HE **[**6,7**]**.

Probiotics have been tested in many studies for hepatic encephalopathy and it has been shown that probiotics significantly improved HE and MHE. Along with it probiotics also had promising results in long-term secondary prophylaxis of HE. **[**8-10**]**. Probiotics enhance the functioning of gut flora resulting in the de-escalation of ammonia production with a resultant decrease in its absorption by decreasing intraluminal pH. Child Pugh's score improves as a result of alteration in short-chain fatty acid production and as a result, endotoxin levels in cirrhotic patients are decreased. Probiotics also provide nutritional benefits to the intestinal epithelial lining by decreasing its permeability and by reducing inflammatory and oxidative stress on liver cells which results in overall increased hepatic ammonia clearance **[**11-13**]**.

Considering the mortality and morbidity associated with hepatic encephalopathy, focus is being shifted towards means to prevent the development of HE which can be achieved with better outcomes with the use of probiotics as opposed to the current conventional regimen. This study aims to conduct an adequately powered trial with better patient selection, well-defined clinical endpoints, and sufficient follow-up

(according to performa) before probiotics can be advanced into an evidence-based treatment and secondary prophylaxis of hepatic encephalopathy.

This study is a comparison of the effectiveness of lactulose alone versus a combination of lactulose plus probiotics for secondary prevention of hepatic encephalopathy in cirrhotic patients.

Material & Methods:

Study Design:

This randomized interventional comparative study was carried out at the Department of Medicine and Gastroenterology, MAYO Hospital, Lahore from April 2016 to August 2018. One hundred sixty-six patients between the ages of 18 & 75 years were included using nonprobability convenient sampling and were randomized to two groups using the lottery method.

Diagnostic Procedures:

Investigations carried out were complete blood count, liver and renal profile, coagulation profile, serum electrolytes, and ultrasound abdomen. Specific investigations included arterial ammonia levels. Diagnosis of liver cirrhosis was made based on clinical assessment, biochemical parameters, and radiological findings. History of illness and the clinical findings after examination were recorded, and the child Pugh score was calculated while screening for enrollment. The clinical presence of hepatic encephalopathy was assessed by psychometric testing and graded by West Haven criteria. Patients with acute liver failure, active alcoholism, hepatocellular carcinoma, chronic kidney disease, history of use of antibiotics (for last 6 weeks), previous history of trans jugular intrahepatic portosystemic shunting (based on relevant history and previous records), psychotropic drug usage (antidepressant, narcotics, sedatives, etc), neurological disease (Alzheimer disease, Parkinson disease, etc) diagnosed based on relevant history and laboratory investigations were excluded.

Data Collection:

Once patients admitted with hepatic encephalopathy of any cause were discharged from the hospital, 166 fulfilling the inclusion criteria were divided into two equal groups using the lottery method.11 In group A patients were given syrup lactulose in an increasing dose according to need up to 120ml daily with the aim

of two to three soft stools/day. In group B, patients were given syrup Lactulose in an increasing dose according to the need for up to 120ml daily with the aim of two to three soft stools per day, along with probiotics **[**Cap. Ecotec 180mg,1 billion CFU (Lactoacidic, Bifidobacterium, S.thermophilus, Lactobulgarius)**]** once daily. Both groups were given treatment for one year and patients were reviewed at regular follow-up intervals every month in the initial 3 months and then 3 monthly. On follow-up visits, patients were questioned about hepatic encephalopathy changes or side effects of the drugs. If an episode of altered sensorium occurred, then history, examination, and appropriate investigations were carried out to rule out possible causes other than hepatic encephalopathy as the cause of altered sensorium. Patients who developed encephalopathy during the said period were labeled as treatment failures and were admitted for treatment as per individual requirements. The absence of hepatic encephalopathy at the end of the study was considered the effective treatment response. The primary endpoint was completing one year or developing hepatic encephalopathy.

Statistical Analysis:

Data was collected on a purposive Excel sheet. Data validation and cleaning were performed on Excel. Collected data were entered into SPSS version 20. Quantitative data like age and grade of hepatic encephalopathy by West Haven criteria were described with mean and standard deviation. Qualitative variables like gender, presence or absence of overt hepatic encephalopathy, compliance rate, and side effect profile of drugs were described as frequencies and percentages. A P-value of less than 0.05 was taken as significant. The compliance rate was determined either by pill counting or supervised drug intake according to the patient's ease and non-compliance was questioned at each follow-up visit as per Performa.

Ethical Considerations:

This study was approved by the institutional review board (IRB) of King Edward medical university vide reference 2183/REG/KEMU/2017. Written informed consent was taken from each patient willing to participate in the study.

Results

Variables, like demographics, the underlying cause of liver disease and its severity, comorbidities, side effects, serum ammonia, compliance, and lost to follow up are shown in Table 1. The response was observed and evaluated in 152 patients who completed the study period. The mean age was 55.84±7.82 and 52.37±6.95 in groups A and B respectively. The majority of patients were of child class B (75.90%) (Figure 1). A total of 152/166 (91.56%) patients completed the study and 14/166 (8.43%) were lost to follow-up. The majority of 110/166, (66.26%) patients had chronic HCV infection as a cause of liver disease (Figure 1). A statistically significant difference was found between serum ammonia levels recorded at baseline and when patients developed hepatic encephalopathy. 14 patients (9 from group A, 5 from group B) failed to follow up, 5 exited the study due to side effects, and 9 due to affordability issues (Table 1). Most of the patients 130(78.31%) were compliant with the correct dosing and timing of medication, while 36(21.68%) patients missed doses due to various reasons like cost, side effects, and forget-ability (Table 1).

Overall encephalopathy occurred in 43(51.80%) and 30(36.14%) of patients in groups A and B respectively (p=0.028) while 31 (37.34%) and 48 (57.83%) completed the study (Table 3). More encephalopathy was observed among relatively older females and patients with child class C. 73(43.97%) patients experienced side effects, 34(40.96%) in group A, and 39(46.98%) in group B (Table 1). Compliance with treatment was seen in patients of groups A and B with similar adverse effects of treatment such as abdominal bloating, distaste, and diarrhea.

All the tests (number connection test, serial dotting test, line tracing test, digital symbol test) were found normal and all patients had zero West Haven grading in both groups at 1st follow-up visit. At 3rd month and 1-year follow-up, the above-enumerated tests were found abnormal in 17(10.2%) and 56 (33.7%) patients respectively while most of the patients had grade 0 West Haven grading followed by grade 3, grade 2, and 4 respectively (Figure2). A statistically significant difference was found between the study groups and tests performed at 1-year follow-up (p=0.025) (Table 2).

Variables		Group A n=83	Group B n=83	*P* value	Total n=166
Age (mean ±SD)		55.83 ±7.63	52.37 ±7.54	*0.09*	N/A
Gender	Male	37 (44.6%)	43 (51.8%)	*0.042*	80(48.2%)
	Female	46 (55.4%)	40 (48.2%)		86(51.8%)
Causes of CLD	HCV	47(56.6%)	63(75.9%)	*0.07*	110(66.3%)
	HBV	26(31.4%)	14(16.8%)		40(24%)
	NBNC	10(12%)	06(7.3%)		16(9.7%)
Child-Pugh class	A	16(19.3%)	14(16.7%)	*0.086*	30(18.1%)
	B	60(72.3%)	66(79.5%)		126(75.9%)
	C	04(4.8%)	06(7.2%)		10(6%)
Co-Morbidities	DM	11(13.25%)	16(19.27%)	*0.028*	27 (16.2%)
	HTN	14(16.86%)	21(25.3%)		35 (21%)
Side effects	Abdominal bloating	27(32.5%)	21(25.3%)	*0.21*	48 (28.9%)
	Diarrhea	19(23%)	14(16.9%)		33 (19.8%)
	Distaste	14 (16.8%)	09 (10.8%)		23 (13.8%)
	Pedal edema	0(0%)	0(0%)		00
Serum Ammonia (mean ±SD)	Baseline	58.95±6.35	59.49±5.93	*0.582*	N/A
	Encephalopathic	83.45±38.15	64.19±20.015	*<0.001*	
Cause of loss to follow up	Side effects	04(4.8%)	01(1.2%)	*0.52*	05
	Affordability issues	05(6%)	04(4.8%)		09
	Others	00(0%)	00(0%)		00
Compliance	YES	63(75.9%)	67(80.7%)	*0.18*	130 (78.3%)
	NO	15(18%)	21(25.3%)		36 (21.68%)

CLD, chronic liver disease; HCV, hepatitis c virus; HBV, hepatitis b virus; NBNC, none hepatitis b none hepatitis c; DM, diabetes mellitus; HTN, hypertension.

Table.1: Demographic variables of the study population (n = 166)

At 1 year 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%)	
West Haven criteria	Grade 0	31(37.3%)	48(57.8%)	79(47.6%)	0.015
	Grade 2	05(6%)	4(4.8%)	9(5.4%)	
	Grade 3	16(19.3%)	9(10.8%)	25(15.1%)	
	Grade 4	11(13.3%)	11(13.3%)	22(13.3%)	

Table.2 Comparison of different test findings at 1 year between study groups

Variables		Study Groups		p-value	Total N=166
		A N=83	B N=83		
Hepatic Encephalopathy	Yes (Failure cases)	43 (51.80%)	30 (36.14%)	0.028	73 (43.97%)
	No (Completed cases)	31 (37.34%)	48 (57.83%)		79 (47.59%)
	Lost follow up	09	05		14 (8.43%)
Symptoms free Male		19 (51.35%)	30 (66.66%)		47 (52.22%)
Symptom-free Female		12 (26.08%)	18 (47.36%)		32 (42.10%)

Table.3 Comparison of results between study groups

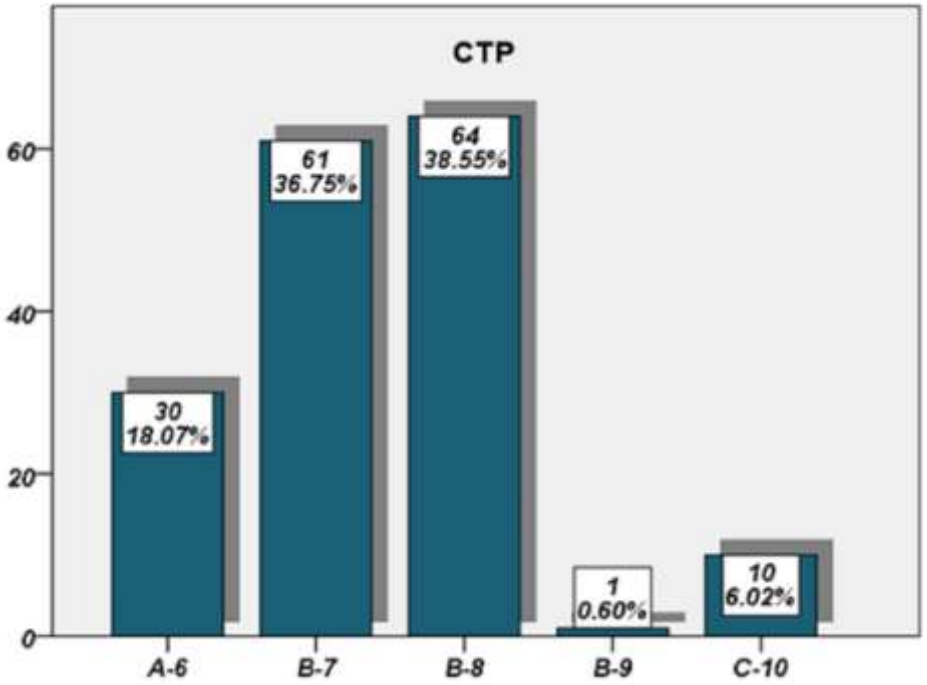

Figure1: Distribution of CTP

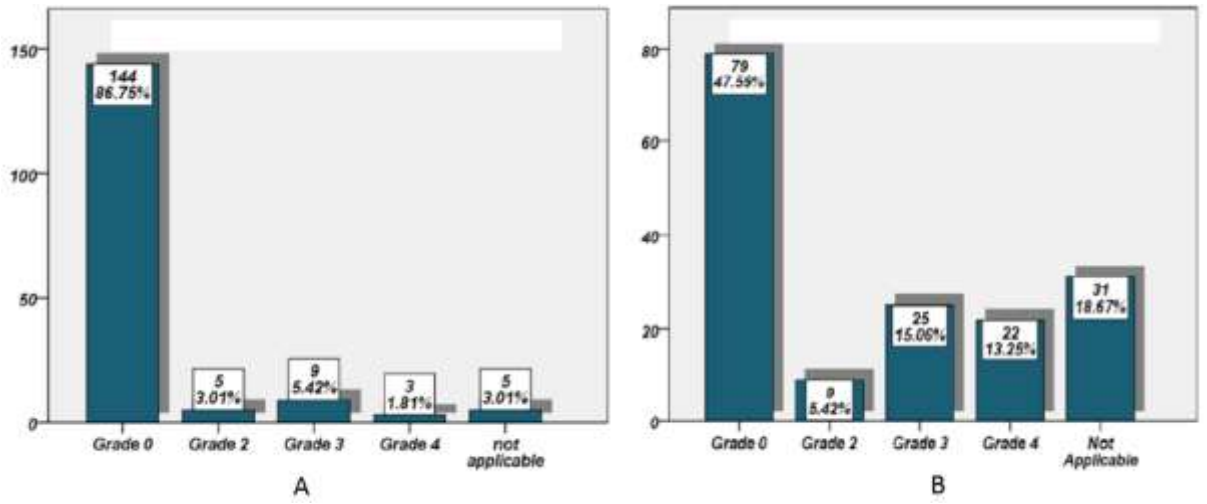

Figure 2: Distribution of West Haven grading. (A) West Haven grading at 3rd month, (B) West Haven grading at 1 year.

Discussion

Dysfunction in the normal physiology of the liver in hepatic encephalopathy gives rise to a grave neuro-psychiatric syndrome that results in a decrepitude central nervous system, especially in decompensated liver disease **[**14,15**]**.

The various benefits and efficacy of probiotics using different strains in the prevention and treatment of encephalopathy have been highlighted in multiple published studies **[**16-22**]**.

Shukla S et al **[**8**]** carried out a meta-analysis after nine studies which revealed better and sustained reversal of HE, and a marked reduction in mortality and hospital stay when probiotics were added to the standard therapy (lactulose). He also observed that probiotics and synbiotics along with lactulose significantly improved minimal hepatic encephalopathy (MHE).

Sharma V et al and Lata J et al in their studies endorsed probiotics proving advantageous in secondary prophylaxis of HE and improvement in MHE in comparison to the current first-line regimen of lactulose and rifaximin. Along with it, they observed that probiotics also help in reducing transaminitis. This comparison included side effects of both treatments and tolerance of medications which revealed probiotics as having better tolerance in patients **[**9,10**]**.

The results of our study primarily focused on the clinical aspects of probiotics in preventing the recurrence of HE. As per our findings, the effective response was seen in 79(47.6%) patients while failure rate was found in 73(44%) patients. Recurrence of HE was more in Lactulose alone group as compared to the combination with the probiotics group, indicating better secondary prophylaxis of HE with the use of probiotics. In addition, our study revealed older patients especially females to be more prone to have a recurrence of HE. Furthermore, we noted constant low levels of serum ammonia in the probiotic combination group which might be due to the beneficial properties of probiotics as explained earlier, hence indirectly preventing HE. It is of great value to see that our analysis is in accord with what we have previously observed in potential studies of patients. According to our analysis, probiotics were generally well tolerated with a negligible number of patients leaving the study due to side effects. Diarrhea, abdominal bloating, and distaste were the commonly observed side effects.

One study by Philip Hendy et al **[**23**]** demonstrated a non-significant benefit of probiotics in the primary outcome, breakthrough HE (p=0.12). However, the grade of HE was significantly lower in the probiotic group (p=0.01). In addition, there was a marked decrease in the number of hospitalizations in patients taking

probiotics (p=0.034), probably due to the episodes being of lesser severity.

Xia X et al **[**18**]** made use of three bacteria in addition to lactic acid bacillus as probiotics in the treatment of hepatic encephalopathy. His statistical analysis showed significant betterment in aberrant psychometric parameters and a marked reduction in blood ammonia levels and the P300 auditory event-related potential. Despite proven benefits in MHE with the use of probiotics, encephalopathy in HBV-related cirrhosis had variable and unclear results to combination therapy of C. butyricum and B. infantis.

Agrawal A et al **[**5**]** conducted a study on secondary prophylaxis in cirrhotic patients for encephalopathy with the use of lactulose, probiotics, or no therapy. The author's study reinforced effectivity of therapy with lactulose and probiotics in the prevention of HE in cirrhotic patients.

Another study by Radha K. Dhiman et al **[**7**]** demonstrated in their study results that there was a decrease in breakthrough HE among patients receiving the probiotic. In addition, it was highlighted that daily use of probiotics over a six-month interval greatly decreased the risk of hospital admissions for HE.

Shavakhi A et al **[**24**]** concluded that a combination of lactulose and probiotics was effective for managing minimal hepatic encephalopathy and more over probiotics have long-term better effects as compared to lactulose. However, more data is required before suggesting probiotics as the preferred treatment choice.

Limitations of the study:

- Small sample size.
- Single-blinded study.
- Carried out at a single center on the same ethnic group.

Conclusion

Our research on patients with cirrhosis who underwent intervention revealed that combining probiotics with lactulose can be beneficial in preventing hepatic encephalopathy in the long term. We compared the effectiveness of lactulose alone with a combination of lactulose and probiotics. The results indicated that the group that received both lactulose and probiotics experienced a greater improvement in hepatic encephalopathy prevention compared to the group that received only lactulose. These findings could have

significant implications for managing patients with cirrhosis who are at risk of developing hepatic encephalopathy.

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