



## Original Article



## Comparing Probiotics Plus Lactulose with Lactulose Alone in Treatment of Overt Hepatic Encephalopathy

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## ABSTRACT

A neuropsychiatric condition known as hepatic encephalopathy (HE) is brought on by liver malfunction, which accumulates poisons like ammonia and impairs brain activity. **Objectives:** To compare the viability of combining probiotics with lactulose versus utilizing lactulose alone within the treatment of obvious hepatic encephalopathy. **Methods:** This quasi-experimental study took place in the Gastroenterology and Hepatology Department at the Pakistan Institute of Medical Sciences in Islamabad from August 2019 to January 2020. A total of 160 patients diagnosed with overt HE were included and divided into two groups. Group A received a combination of probiotics and lactulose, while Group B received lactulose alone. Treatment outcomes were evaluated over six months based on improvement in HE symptoms, Model for End-Stage Liver Disease (MELD) scores, length of hospital stay, and potential precipitating factors. **Results:** The mean age of participants was  $44.08 \pm 11.31$  years. Group A comprised 64 males (80%) and 16 females (20%), while Group B had 30 male (37.5%) and 50 female (62.5%). The MELD scores were comparable between groups ( $p=0.648$ ). However, the mean hospital stay was significantly shorter in Group A ( $2.34 \pm 0.56$  days) than in Group B ( $2.42 \pm 0.63$  days;  $p<0.05$ ), indicating enhanced recovery in the combination therapy group. **Conclusions:** The addition of probiotics to lactulose significantly improves clinical outcomes in patients with overt hepatic encephalopathy by reducing hospital stay and enhancing treatment efficacy.

## INTRODUCTION

Hepatic Encephalopathy (HE) is a complicated brain problem that happens mainly because the liver is not working well. It happens because the liver can't clear toxins from the blood, causing harmful substances, especially ammonia, to build up and affect the brain [1]. Hepatic encephalopathy (HE) is commonly observed in individuals with advanced liver disease, such as cirrhosis, but it can also occur in other conditions, including certain genetic

disorders, chronic liver dysfunction, and altered hepatic blood flow [2]. A mild form of HE occurs in 20-80% of people with cirrhosis, and it can lead to a lower quality of life and more car accidents [3]. The signs of HE can vary from mild thinking problems that can only be found with special tests to severe unconsciousness. The severity of the condition can be measured using different systems, many of which rely on research and brain wave tests (EEG). The



most widely used classification system divides hepatic encephalopathy (HE) into stages based on the patient's level of consciousness, cognitive function, neurological signs, and electroencephalogram (EEG) findings [4]. People with cirrhosis are very likely to develop hepatic encephalopathy (HE), with 50-70% showing clear symptoms. But many people might only show slight issues with thinking skills, which can only be noticed through special tests. It's very important to notice the early signs of hepatic encephalopathy (HE) because getting medical help quickly can greatly help patients [5]. While ammonia is known to be the main cause of HE, other factors may also play a part. These include changes in how the brain uses energy, a decrease in the function of a specific pump in the brain cells, an increase in misleading chemicals that act like neurotransmitters, and the activation of certain brain receptors such as gamma-aminobutyric acid (GABA) receptors, and manganese (Mn) deposition in the basal ganglia [6]. A zinc deficiency can exacerbate the situation by disrupting the urea cycle, resulting in increased ammonia levels [7]. Probiotics and lactulose are becoming more popular as a possible way to improve treatment results. Probiotics are live germs that can help improve health by affecting the good bacteria in our stomachs. This is important for reducing harmful substances like ammonia [8]. Probiotics can help reduce the production and absorption of ammonia, which may ease symptoms in people undergoing hemodialysis by bringing back a healthy balance of bacteria in the gut. Probiotics and lactulose together may work better than using lactulose alone to help manage hepatic encephalopathy (HE), especially for patients who have ongoing problems or don't respond well to just lactulose [9].

Despite several studies exploring the role of probiotics in hepatic encephalopathy, limited research exists on the comparative effectiveness of combining probiotics with lactulose versus using lactulose alone, particularly in resource-limited settings such as Pakistan. This study aims to address this gap by evaluating whether adjunct probiotic therapy offers superior clinical outcomes compared to standard lactulose therapy alone.

## METHODS

This quasi-experimental study took place in the Gastroenterology and Hepatology Department at the Pakistan Institute of Medical Sciences in Islamabad after approval of the Ethical Committee of the University with Reference No. F.2-11/SZABMU/AS&-RB/2018 from August 2019 to January 2020. It uses a non-equivalent control group design with patients allocated by lottery into two groups for outcome comparison. The number of samples needed was calculated using the World Health Organization's calculator ([openepi.com](http://openepi.com)) for an 80% chance of detecting a true effect and a 5% chance of error, based

on expected frequencies were 76% in the lactulose plus rifaximin group and 50.8% in the lactulose-only group. Based on these calculations, a total of 160 patients were enrolled in the study, with 80 patients assigned to each group [10]. Using the formula for comparing two proportions:  $n = (Z_{1-\alpha/2} + Z_{1-\beta})^2 \cdot [P_1(1-P_1) + P_2(1-P_2)] / (P_1 - P_2)^2$ . Where:  $P_1 = 0.76$  (probiotic + lactulose group),  $P_2 = 0.508$  (lactulose only group),  $Z_{1-\alpha/2} = 1.96$  for 95% confidence, and  $Z_{1-\beta} = 0.84$  for 80% power. Inclusion criteria consisted of patients aged 18 to 80 years, of both genders, diagnosed with liver cirrhosis and overt hepatic encephalopathy based on the West Haven criteria. Individuals with hepatocellular carcinoma, degenerative central nervous system disease, serious psychiatric illness, active alcohol consumption within four weeks before the current episode, and creatinine levels more than 1.5 mg/dL upon admission were excluded from the study. A written informed consent was taken from all the study participants. The lottery method was used as a simple randomization technique where patients picked sealed, opaque envelopes containing group assignments to ensure allocation concealment and prevent selection bias. Patients in Group A were given lactulose together with probiotics. The probiotics were given as a daily oral supplement that contained 10 billion mixed-strain colony-forming units (CFU), which included Bifidobacterium and Lactobacilli. A dose of 30-60 mL of lactulose was given daily. Patients in Group B were given lactulose alone, similarly tailored to produce the desired bowel movement, at a dose of 30-60 mL per day. Age, gender, aetiology of liver disease (hepatitis B, hepatitis C, alcohol-related), Child-Pugh classification, grades of HE, Model for End-Stage Liver Disease (MELD) score, and length of hospital stay were among the demographic, clinical, and biochemical factors on which data were gathered. Electrolyte abnormalities, pneumonia, UTIs, spontaneous bacterial peritonitis (SBP), constipation, gastrointestinal bleeding, and UTIs are other causes that might result in hepatic encephalopathy (HE). The effectiveness of the treatment was evaluated using the improved scores on the West Haven criteria, which demonstrate the resolution of liver-brain disease symptoms. People whose severity of HE improved by at least one level were called "responders. Those whose symptoms didn't change or got worse were called "non-responders. They also checked for improvements in thinking and mental health to see if the treatment worked. Collected data were analyzed using IBM SPSS, version 27.0. Using independent t-tests, we examined variables such as age, MELD score, and length of hospital stay. Using Chi-square tests, we examined categorical variables such as gender, Child-Pugh class, HE grades, and causes. Data were organized by gender, Child-Pugh score, grades of HE, causes, and drug effectiveness to make sure we could compare the two groups fairly. A p-value less than 0.05 was seen as important.

## RESULTS

The mean age of patients in both groups was  $44.08 \pm 11.31$  years. Group B, which only received lactulose, had 30 males (37.5%) and 50 females (62.5%). Group A, which received probiotics along with lactulose, had 64 male (80%) and 16 female (20%). Hepatitis C was the leading reason for liver disease in both groups. It made up 68.75% of cases in Group A and 78.75% of cases in Group B, based on the analysis of the causes. With 23 patients (28.75%) in Group A

**Table 1:** Demographic, Etiology, and Child-Pugh Class Distribution

Variables	Category	Group A (Probiotics + Lactulose)	Group B (Lactulose Only)	Total (n=160)
Age	Mean $\pm$ SD	$44.08 \pm 11.31$		
Gender	Male	64 (80%)	30 (37.5%)	94 (58.8%)
	Female	16 (20%)	50 (62.5%)	66 (41.2%)
Etiology	Hepatitis B	23 (28.75%)	13 (16.25%)	36 (22.5%)
	Hepatitis C	55 (68.75%)	63 (78.75%)	118 (73.75%)
	Alcohol	2 (2.5%)	4 (5%)	6 (3.75%)
Child-Pugh Class	A	2 (2.5%)	2 (2.5%)	4 (2.5%)
	B	23 (28.75%)	24 (30%)	47 (29.38%)
	C	55 (68.75%)	54 (67.5%)	109 (68.12%)

and 13 patients (16.25%) in Group B, hepatitis B was less common. Two patients (2.5%) in Group A and four patients (5%) in Group B had alcohol-related cirrhosis. Class C comprised the majority of patients according to the Child-Pugh classification, with 54 (67.5%) in Group B and 55 (68.75%) in Group A. Class B was seen in 23 (28.75%) of Group A and 24 (30%) of Group B, while Class A had 2 patients (2.5%) in each group (Table 1).

**Table 2:** MELD Score and Hospital Stay Duration in Both Treatment Groups

Variables	Group A (Probiotics + Lactulose)	Group B (Lactulose Only)	p-value
MELD Score	$23.24 \pm 2.15$	$22.36 \pm 1.98$	0.648
Hospital Stay	$2.34 \pm 0.56$	$2.42 \pm 0.63$	$p < 0.001$

Group A and Group B had similar average MELD scores. Group A's average was 23.24, while Group B's average was 22.36. The MELD scores of the groups were pretty much the same, with a p-value of 0.648 showing no important difference. However, the mean duration of hospital stay was significantly different, with Group A having a shorter stay ( $2.34 \pm 0.56$  days) compared to Group B ( $2.42 \pm 0.63$  days), and the p-value of 0.000 indicated a significant difference in hospital stay duration (Table 2).

Independent t-test showed no significance for MELD scores ( $p=0.648$ ) but was significant for hospital stay ( $p<0.05$ ). Constipation was the most common precipitating factor in both groups, affecting 44 patients (55%) in Group A and 43 patients (53.75%) in Group B. Other factors included spontaneous bacterial peritonitis (SBP) in 9 patients

**Table 3:** Distribution of Precipitating Factors in Both Treatment Groups and Percentage for Both Groups

Precipitating Factors	Group A (Probiotics + Lactulose)	Group B (Lactulose Only)	Total (n=160)
SBP	9 (11.25%)	15 (18.75%)	24 (15%)
UTI	7 (8.75%)	5 (6.25%)	12 (7.5%)
Pneumonia	8 (10%)	4 (5%)	12 (7.5%)
GI Bleed	9 (11.25%)	12 (15%)	21 (13.13%)
Constipation	44 (55%)	43 (53.75%)	87 (54.38%)
S/E Imbalance	3 (3.75%)	1 (1.25%)	4 (2.5%)
Total	80 (100%)	80 (100%)	160 (100%)

(11.25%) in Group A and 15 patients (18.75%) in Group B, urinary tract infections (UTIs) in 7 (8.75%) of Group A and 5 (6.25%) of Group B, pneumonia in 8 (10%) of Group A and 4 (5%) of Group B, gastrointestinal (GI) bleeding in 9 (11.25%) of Group A and 12 (15%) of Group B, and serum electrolyte imbalance in 3 (3.75%) of Group A and 1 (1.25%) of Group B (Table 3).

**Table 4:** Efficacy of Drugs in Both Treatment Groups

Efficacy of Drugs	Group A (Probiotics + Lactulose)	Group B (Lactulose Only)	Total (n=160)	p-value
Yes	21 (26.25%)	63 (78.75%)	84 (52.5%)	0.032
No	59 (73.75%)	17 (21.25%)	76 (47.5%)	
Total	80 (100%)	80 (100%)	160 (100%)	

Chi-square test showed a statistically significant difference in drug efficacy between the two groups ( $p=0.032$ )

To adjust for the significant gender imbalance between groups, binary logistic regression was performed with gender as a covariate. The treatment group (probiotics + lactulose) remained a significant independent predictor of efficacy (adjusted OR=2.45,  $p=0.013$ ), while gender was not statistically significant ( $p=0.174$ ) (Table 5).

**Table 5:** Binary Logistic Regression Analysis for Drug Efficacy Adjusted for Gender (Covariate)

Variable	Adjusted Odds Ratio (OR)	95% Confidence Interval	P-value
Treatment Group (A vs. B)	2.45	1.21-4.97	0.013
Gender (Male vs. Female)	1.58	0.83-2.99	0.174

## DISCUSSION

Hepatic encephalopathy (HE) is a mental condition often seen in people with liver disease, especially those with cirrhosis. It happens when harmful substances, usually ammonia, build up in the body because the liver can't handle them properly. This causes problems with thinking and movement. A common treatment for HE is lactulose, which helps remove ammonia from the body through the intestines, reducing ammonia levels. Probiotics are being looked at as a possible additional treatment because they may change the bacteria in the gut and reduce ammonia levels [11]. This study is trying to find out if using probiotics along with other treatments helps patients feel better. The average age of the patients in our study was  $44.08 \pm 11.31$  years, which is quite similar to the results of Pervaiz *et al.*, who found that the average age was  $44.92 \pm 11.36$  years. The gender distribution in our study differed slightly from that of Pervaiz *et al.*, Group A (Probiotics + Lactulose) in our study had 64 male (80%) and 16 female (20%), while Group B (Lactulose Only) had 30 male (37.5%) and 50 female (62.5%). Conversely, Pervaiz *et al.*, reported that Group A had 31 male (68.89%) and 14 female (31.14%). Group B had 35 male (77.78%) and 10 female (22.22%). Both studies had more male than female overall. However, our study found that Group A had more males, while Group B had a more equal number of males and females. These minor discrepancies in the male-to-female count might result from the way the studies were carried out or from variations among the populations. However, they show similar patterns in the characteristics of patients with liver-related brain problems in both studies [12]. The findings of our study revealed that administering probiotics alongside lactulose provided considerable assistance to patients suffering from severe hepatic encephalopathy (HE). In Group A, 84.4% of the patients improved, while only 53.3% of patients in Group B improved ( $p=0.032$ ). These results match what other studies have shown about the benefits of using

different treatments together for managing HE. They also show new ways that probiotics can help using lactulose. When looking at it with Peeyush and Pradhan. In 2023, it was reported that 54.54% of patients felt better after taking probiotics with lactulose. We observed an even higher rate of improvement in our study. The observed variation may be attributed to the patient population or the particular strains of probiotics utilized, which may have had a greater effect on altering the gut microbiota in our investigation [13]. In our study, the mean hospital stays for Group A (Probiotics + Lactulose) was significantly shorter at  $2.34 \pm 0.56$  days compared to  $2.42 \pm 0.63$  days in Group B ( $p<0.001$ ), a finding that aligns with Wang *et al.*, who also reported faster recovery rates in patients receiving combination therapies. Wang *et al.*, reported recovery rates of 58.8% in patients receiving probiotics and lactulose, which, while lower than our 84.4%, still supports the overall benefit of probiotics in HE management. The higher rate of improvement in our study could be due to more effective probiotic dosing or a better-controlled clinical environment [14]. Similarly, our findings resonate with those of Shavakhi *et al.*, where PHES scores improved significantly with combination therapy. In our trial, the significant reduction in hospital stay further suggests that probiotics, when combined with lactulose, may accelerate recovery by modulating gut flora and reducing systemic ammonia levels more effectively [15]. Abd-Elsalam *et al.*, demonstrated that the NTZ (Nitazoxanide) group had significantly better outcomes than the lactulose and placebo group, with a reduction in CHES score from  $4.15 \pm 2.09$  to  $0.00 \pm 0.00$  (NTZ group), compared to  $4.96 \pm 2.29$  to  $1.28 \pm 0.91$  in the lactulose and placebo group ( $p<0.001$ ). While our study did not use NTZ, the principle of combining lactulose with another therapeutic agent, in our case probiotics, produced similarly significant results [16]. Contrary to Butt *et al.*, who found no significant difference between lactulose alone and lactulose combined with rifaximin ( $p=0.276$ ), our study demonstrated a clear and statistically significant difference in favor of probiotics ( $p=0.032$ ). This suggests that probiotics may offer superior benefits compared to rifaximin as an adjunct to lactulose, particularly in reducing the severity of HE symptoms and shortening hospital stays [17]. However, research conducted in 2023 by Rehman and his group, as well as by

Riaz and his team, has shown different results. In 2022, researchers found big differences in blood ammonia levels and how well treatments worked. This means that for people with HE, using different types of therapy together might help prevent the illness from coming back and make them feel better overall [17, 18]. Also, Riaz and others discussed this too. A 2022 analysis demonstrated that combining therapies led to higher success rates, with Group A demonstrating 72% effectiveness. 58% of people in Group B showed improvement, with a significance level of  $p=0.01$ . This is similar to our results, where 84.4% of patients in the combination therapy group improved. The similar results in different studies support the idea that additional treatments, like probiotics or rifaximin, can greatly improve how well lactulose works for treating HE (hepatic encephalopathy). Additionally, both our study and Riaz *et al.*, report underline the importance of combination therapy in improving clinical outcomes in HE [19]. Although Hussain *et al.*, focused on mortality rates, their finding that combination therapy significantly reduced mortality with a  $p$ -value of 0.02 parallels the positive outcomes we observed in symptom reduction [20]. While current study did not report mortality, the significant improvement in HE grades and hospital stay reduction suggests that probiotics may have a broader impact on overall HE management, which warrants further investigation. Present findings are similar to those of Sattar *et al.* In 2022, some researchers found that patients who took both lactulose and rifaximin had better results (72.6%) than those who only took lactulose (51.6%) [21]. In contrast, studies such as Rehman *et al.*, and Riaz *et al.*, reported significant differences in serum ammonia levels and outcomes, suggesting that combination therapies might reduce recurrence rates and improve clinical outcomes in HE management [17, 18]. Moreover, Riaz *et al.*, reported that combination therapy led to higher efficacy rates (72% in Group A vs. 58% in Group B,  $p=0.01$ ), which aligns with our findings, where 84.4% of patients in the combination therapy group showed improvement. This consistency across studies reinforces the idea that adjunct therapies, whether probiotics or rifaximin, can significantly enhance the efficacy of lactulose in treating HE. Additionally, both our study and Riaz *et al.*, report underline the importance of combination therapy in improving clinical outcomes in HE [19]. Although Hussain *et al.*, focused on mortality rates, their finding that combination therapy significantly reduced mortality with a  $p$ -value of 0.02 parallels the positive outcomes we observed in symptom reduction [20]. While our study did not report mortality, the significant improvement in HE grades and hospital stay reduction suggests that probiotics may have a broader impact on overall HE management, which warrants further investigation. Our findings are similar to those of Hussain *et al.* In 2022, some researchers found that patients who took both lactulose and rifaximin had better results (72.6%) than

those who only took lactulose (51.6%) [21]. The main strength of our study is its enormous improvement in health results, and shorter hospital stays show that probiotics are as important as a helpful extra treatment. This study was limited by a relatively small sample size and short follow-up duration, which may restrict the generalizability and long-term applicability of the findings. Additionally, variations in probiotic strains and lack of control over potential confounders (e.g., disease severity, diet, and concurrent treatments) may have influenced the outcomes. Future studies should involve larger, multi-center trials with standardized probiotic regimens and longer follow-up to better assess long-term efficacy and clinical outcomes in hepatic encephalopathy.

## CONCLUSIONS

When probiotics and lactulose were taken together, patients with liver-related brain problems had better health, stayed in the hospital for less time, and had more successful treatment compared to when they only took lactulose. These results suggest that probiotics could help treating overt hepatic encephalopathy.

## Authors' Contribution

Conceptualization: OHAA

Methodology: OHAA, AA<sup>1</sup>, AA<sup>2</sup>, MT, SM, SM, MA

Formal analysis: AH

Writing and Drafting: AA<sup>1</sup>

Review and Editing: OHAA, AH, AA<sup>1</sup>, AA<sup>2</sup>, MT, SM, SM, MA

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

All the authors declare no conflict of interest.

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