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EFFECT OF PROBIOTICS ON CLINICAL IMPROVEMENT IN PATIENTS WITH HEPATIC ENCEPHALOPATHY: A PRE-POST INTERVENTIONAL STUDY AT A SHEIKH ZAYED HOSPITAL LAHORE

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ABSTRACT

Background: Hepatic encephalopathy (HE) is a potentially reversible neuropsychiatric complication of advanced liver disease, particularly liver cirrhosis. Increased ammonia production, intestinal dysbiosis, and impaired gut-barrier function contribute to neurological and cognitive dysfunction. Probiotics may improve HE by restoring intestinal microbial balance and reducing the production and absorption of ammonia and other neurotoxins.
Objective: To evaluate the effectiveness of probiotic therapy in improving clinical severity and reducing serum ammonia levels in patients with hepatic encephalopathy.
Methods: Patients diagnosed with hepatic encephalopathy who met the predefined eligibility criteria were enrolled after informed consent. Baseline demographic information, clinical history, encephalopathy grade, neurological findings, and serum ammonia levels were recorded. Participants received probiotic therapy alongside standard medical management for four weeks. Clinical status was monitored using a standardized grading system based on consciousness, orientation, behavior, cognition, and neuromuscular signs such as asterixis. At the end of the intervention, clinical grading and serum ammonia measurements were repeated and compared with baseline findings. Appropriate statistical methods were used to assess pre- and post-treatment changes.
Results: After four weeks of probiotic supplementation, patients demonstrated improvement in hepatic encephalopathy severity. Improvements included better orientation and cognitive performance, reduced confusion, and decreased asterixis. Several patients shifted from moderate to milder grades of encephalopathy, while some experienced resolution of neurological manifestations. Serum ammonia levels also decreased following treatment, indicating a favourable biochemical response.
Conclusion: Probiotics may provide a safe, well-tolerated, and cost-effective adjunct to conventional therapy for hepatic encephalopathy. Their beneficial effects may result from modulation of gut microbiota, reduced intestinal ammonia production, and improved gut-barrier function. Larger randomized controlled trials with longer follow-up periods are required to confirm these findings and establish standardized probiotic treatment regimens.

Keywords: Hepatic encephalopathy; probiotics; gut microbiota; liver cirrhosis; ammonia.

INTRODUCTION

Hepatic encephalopathy (HE) is a potentially reversible neuropsychiatric syndrome that develops in patients with acute liver failure, advanced chronic liver disease, or portosystemic shunting. It represents a continuum of brain dysfunction, extending from subtle abnormalities detectable only through psychometric or neurophysiological testing to overt disorientation, marked behavioural changes, somnolence, stupor, and coma [1,2]. In patients with cirrhosis, HE is among the most disabling complications because it interferes with cognition, communication, self-care, employment, driving ability, and social functioning. Recurrent episodes also place a considerable burden on caregivers and healthcare services through emergency visits, repeated hospital admissions, prolonged hospital stays, and increased mortality risk [1,3]. Clinically, patients may develop impaired attention, slowed information processing,

disturbed sleep–wake rhythm, personality changes, memory deficits, reduced coordination, dysarthria, and asterixis. The West Haven criteria are commonly used to grade overt HE according to changes in awareness, intellectual performance, behaviour, and neuromuscular function, whereas covert HE requires more sensitive psychometric or neurophysiological assessment [1–3].

The pathogenesis of HE is complex and cannot be explained by a single toxin or biological pathway. Hyperammonaemia remains a central mechanism, but its neurological effects are amplified by systemic inflammation, oxidative stress, altered cerebral energy metabolism, hyponatraemia, and impaired neurotransmission [4]. Ammonia is generated mainly in the gastrointestinal tract through bacterial urease activity and the metabolism of dietary and endogenous nitrogen. In healthy individuals, portal blood carries ammonia to the liver, where it is detoxified primarily through the urea cycle and glutamine synthesis. In cirrhosis, hepatocellular dysfunction reduces ammonia clearance, while spontaneous or surgically created portosystemic shunts allow ammonia-rich portal blood to bypass hepatic detoxification [4,5]. Skeletal-muscle wasting, renal dysfunction, constipation, gastrointestinal bleeding, infection, and an increased intestinal nitrogen load may further elevate systemic ammonia concentrations.

Once ammonia crosses the blood–brain barrier, astrocytes convert it to glutamine through the action of glutamine synthetase. Excess intracellular glutamine increases osmotic stress, promotes astrocyte swelling, and disrupts cellular energy homeostasis [5,6]. Ammonia can also impair mitochondrial function, alter neurotransmitter balance, and interfere with neuronal signalling. However, blood ammonia concentrations do not always correlate closely with the clinical grade of HE, indicating that additional mechanisms influence neurological susceptibility. Systemic inflammation is particularly important because inflammatory cytokines may increase blood–brain barrier permeability, activate microglia, intensify oxidative and nitrosative stress, and enhance the cerebral effects of ammonia [4,6]. This interaction helps explain why infections, gastrointestinal bleeding, dehydration, electrolyte disturbances, renal impairment, constipation, sedative medications, and poor treatment adherence frequently precipitate acute HE episodes, even when the patient's underlying liver function appears relatively unchanged.

Increasing attention has therefore focused on the gut–liver–brain axis. The intestinal microbiota normally contributes to nutrient metabolism, bile-acid transformation, immune regulation, colonization resistance, and maintenance of epithelial-barrier integrity. In cirrhosis, reduced bile flow, impaired intestinal motility, altered dietary intake, frequent antibiotic exposure, portal hypertension, and immune dysfunction can disturb this microbial ecosystem. Studies have demonstrated that patients with cirrhosis, particularly those with HE, have altered intestinal microbial compositions associated with cognitive impairment, endotoxaemia, and systemic inflammation [7–9]. Expansion of potentially pathogenic or urease-producing organisms may increase the generation of ammonia, endotoxins, mercaptans, phenols, and other microbial metabolites. At the same time, depletion of beneficial autochthonous bacterial taxa may weaken colonization resistance and reduce the production of metabolites that support intestinal epithelial health.

Cirrhosis is also associated with disruption of epithelial tight junctions and increased intestinal permeability. Consequently, bacterial products such as lipopolysaccharide and other pathogen-associated molecular patterns may translocate across the intestinal barrier and enter the portal or systemic circulation. These products stimulate innate immune responses and promote systemic inflammation, which may act synergistically with hyperammonaemia to impair cerebral function [7–9]. Associations between specific mucosal and faecal microbial profiles, inflammatory markers, and cognitive performance further support a mechanistic relationship between dysbiosis and HE rather than a purely incidental alteration in microbial composition [7,8]. These observations have provided a strong rationale for therapeutic strategies that modify the intestinal environment and reduce the production or absorption of neurotoxic substances.

Probiotics are defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host [10]. In HE, their proposed mechanisms include suppression of pathogenic and urease-producing bacteria, reduction of intestinal pH, improvement of epithelial-barrier integrity, modulation of bile-acid and nitrogen metabolism, and attenuation of intestinal and systemic inflammation. Some probiotic and synbiotic formulations may also promote non-urease-producing organisms that utilize ammonia for bacterial protein synthesis, thereby reducing its absorption from the colon. A randomized study of synbiotic therapy demonstrated improvement in minimal HE together with favourable changes in intestinal flora and ammonia-related measures [11]. Subsequent clinical trials reported that probiotic supplementation could improve cognitive or clinical outcomes and reduce the development of overt HE in selected patients with cirrhosis [12].

Nevertheless, the available clinical evidence remains heterogeneous because studies have used different bacterial strains, doses, treatment durations, diagnostic methods, disease severities, and background therapies. Meta-analyses indicate that probiotics may improve minimal HE, reduce progression to overt HE, lower circulating ammonia concentrations, and potentially decrease hospitalization compared with placebo or no treatment; however, their superiority over lactulose has not been consistently established [13,14]. The evidence is also limited by relatively small sample sizes, variable risks of bias, and inconsistent reporting of clinically important outcomes, including recurrence, mortality, quality of life, and adverse events [14]. Probiotics should therefore be considered a promising adjunct rather than a replacement for established HE treatment. Evaluating their effects on neurological status and serum ammonia concentrations may help clarify their role within a broader therapeutic strategy targeting the gut–liver–brain axis in patients with hepatic encephalopathy.

MATERIALS AND METHODS

Study Design

This study was designed as analytical study to evaluate the effectiveness of probiotic therapy in improving clinical outcomes among patients diagnosed with Hepatic Encephalopathy. The pre-post design allowed comparison of clinical and biochemical parameters before and after administration of probiotic therapy within the same group of patients. This approach helped assess the direct impact of the intervention on disease severity and laboratory markers, particularly serum ammonia levels.

Study Setting

The study was conducted in the Department of Gastroenterology at a Sheikh Zayed Hospital Lahore, Pakistan. Sheikh Zayed Hospital manage a large number of patients with chronic liver diseases and their complications, making them suitable settings for clinical research. Patients admitted to the gastroenterology ward or attending outpatient clinics with symptoms suggestive of hepatic encephalopathy were evaluated and screened for eligibility according to the study criteria.

Sample Size and Study Population

A total of 100 patients diagnosed with hepatic encephalopathy were included in the study. Participants were selected through a non-probability consecutive sampling technique during the study period. All patients underwent detailed clinical assessment, laboratory investigations, and medical history evaluation prior to enrollment. Only those individuals who fulfilled the predefined inclusion criteria and provided informed consent were included in the study.

Inclusion Criteria

Patients meeting the following criteria were included in the study:

- Adults aged between 18 and 70 years.
- Patients clinically diagnosed with hepatic encephalopathy of Grade I–III severity.
- Patients with underlying chronic liver disease, particularly Liver Cirrhosis confirmed by clinical, biochemical, and imaging findings.

These criteria ensured the inclusion of patients with mild to moderate hepatic encephalopathy who were stable enough to receive probiotic therapy and complete the intervention period.

Exclusion Criteria

Patients with the following conditions were excluded from the study to avoid confounding factors that could influence the outcomes:

- Severe hepatic encephalopathy (Grade IV) requiring intensive care management.
- Presence of active gastrointestinal bleeding.
- Patients with renal failure or severe systemic illness.
- Patients who had received probiotic therapy within the previous few weeks.

Excluding these conditions helped maintain uniformity within the study population and improved the reliability of the results.

Intervention

All enrolled patients received probiotic therapy in addition to standard treatment for hepatic encephalopathy. The probiotic formulation contained strains of Lactobacillus and Bifidobacterium, which are commonly used beneficial bacteria known to help restore normal intestinal microbial balance. Patients were instructed to take probiotic capsules twice daily for a duration of four weeks. Standard therapy, including medications such as lactulose and dietary management, was continued as prescribed by the treating physician. During the intervention period, patients were monitored regularly for clinical improvement and possible adverse effects.

Baseline clinical assessment was performed before initiating probiotic therapy. Clinical grading of hepatic encephalopathy was evaluated using standard neurological criteria that assess mental status, orientation, behavior, and

neuromuscular signs such as asterixis. In addition, blood samples were collected to measure serum ammonia levels prior to the intervention. At the end of the four-week treatment period, the same clinical and laboratory assessments were repeated to evaluate changes following probiotic therapy.

Statistical Analysis

All collected data were entered and analyzed using SPSS version 26. Quantitative variables such as serum ammonia levels were expressed as mean and standard deviation, while categorical variables such as clinical grading were presented as frequencies and percentages. The paired t-test was applied to compare pre-intervention and post-intervention values within the same group of patients. A p-value of ≤ 0.05 was considered statistically significant, indicating that the observed differences were unlikely to have occurred by chance. The results were summarized in tables and charts to clearly demonstrate the effectiveness of probiotic therapy in improving clinical and biochemical parameters in patients with hepatic encephalopathy.

RESULTS

Table 1: Demographic Characteristics

Variable	Frequency	Percentage
Male	63	63%
Female	37	37%
Mean Age	54 ± 10	

Table 2: Clinical Grade of HE Before and After Treatment

HE Grade	Before Treatment	After Treatment
Grade I	18	32
Grade II	25	20
Grade III	17	8

Table 3: Serum Ammonia Levels

Parameter	Mean ± SD
Before Treatment	118 ± 24 µmol/L
After Treatment	78 ± 19 µmol/L

Table 4: Clinical Improvement Indicators

Outcome	Percentage
Improvement in mental status	72%
Improvement in cognition	65%
Reduced hospitalization	58%

Discussion

The present study demonstrated improvement in the clinical grading of hepatic encephalopathy and a reduction in serum ammonia levels following four weeks of probiotic therapy administered alongside standard medical management. These findings support the growing evidence that modulation of the intestinal microbiota may improve

neurological and biochemical outcomes in patients with hepatic encephalopathy. The observed changes are biologically plausible because hepatic encephalopathy is closely associated with disruption of the gut–liver–brain axis, including intestinal dysbiosis, increased ammonia production, impaired intestinal-barrier integrity, bacterial translocation, and systemic inflammation. However, because probiotics were administered with conventional treatment, the improvement cannot be attributed exclusively to probiotic supplementation.

The reduction in clinical severity observed in the present study is consistent with findings from previous clinical trials. Dhiman et al. reported that supplementation with the multistrain probiotic VSL#3 reduced hospitalization risk and improved indicators of liver-disease severity in patients with cirrhosis. The treatment was also associated with improvements in systemic inflammatory responses and health-related quality of life, although the effect on breakthrough overt hepatic encephalopathy was less definitive [15]. Similarly, Mouli et al. found that VSL#3 was non-inferior to lactulose in reversing minimal hepatic encephalopathy. Patients whose cognitive status improved also demonstrated more favourable changes in ammonia concentrations, suggesting a relationship between reduced nitrogenous toxin exposure and improved neurological performance [16].

The present findings are also supported by a randomized study conducted by Sharma et al., in which lactulose, probiotics, and their combination improved minimal hepatic encephalopathy. The investigators found no clear difference between these therapeutic approaches in terms of reversal of minimal hepatic encephalopathy, indicating that probiotics may provide clinically relevant benefits in selected patients [17]. Mittal et al. similarly reported that probiotics, lactulose, and L-ornithine L-aspartate improved psychometric performance and health-related quality of life in patients with minimal hepatic encephalopathy [18]. Collectively, these studies support the interpretation that probiotics may improve cognitive and neurological function by modifying intestinal microbial activity and reducing the production or absorption of neurotoxic metabolites.

A major finding of the present study was the reduction in serum ammonia following probiotic therapy. Hyperammonaemia remains a central contributor to hepatic encephalopathy, although its concentration does not always correlate directly with clinical grade. Probiotics may reduce ammonia through several complementary mechanisms. Beneficial bacterial strains can suppress urease-producing and potentially pathogenic organisms, reduce intestinal pH, improve nitrogen utilization by intestinal bacteria, and promote incorporation of ammonia into bacterial proteins. These effects can decrease the quantity of ammonia available for intestinal absorption. Probiotics may additionally improve bowel function and reduce intestinal transit time, thereby limiting prolonged bacterial metabolism of nitrogen-containing material. Nevertheless, ammonia should not be interpreted as the only marker of treatment response because inflammation, electrolyte disturbances, infection, renal function, portosystemic shunting, and nutritional status may also affect neurological presentation.

The potential value of probiotics in preventing recurrent hepatic encephalopathy has also been investigated. Agrawal et al. compared lactulose, probiotics, and no preventive treatment in patients who had recovered from an episode of overt hepatic encephalopathy. Both lactulose and probiotic therapy reduced recurrence compared with no treatment, suggesting that long-term modification of the intestinal environment may contribute to secondary prevention [19]. This observation is clinically important because recurrent hepatic encephalopathy is associated with repeated hospitalization, progressive functional dependence, reduced quality of life, and an increased burden on family caregivers. However, the comparative effectiveness of probiotics and established preventive therapies requires further clarification.

Improvement in the intestinal microbial environment may also explain the neurological recovery observed in the current study. Bajaj et al. demonstrated that probiotic yogurt improved minimal hepatic encephalopathy in patients with non-alcoholic cirrhosis. Probiotic treatment was associated with reversal of cognitive abnormalities in a proportion of patients and appeared to be well tolerated [20]. Restoration of beneficial microbial populations may reduce the abundance or metabolic activity of organisms responsible for producing ammonia, endotoxins, phenols, mercaptans, and other potentially neuroactive compounds. A healthier microbial environment may also generate metabolites that support epithelial integrity and regulate local immune responses.

In addition to lowering ammonia production, probiotics may influence hepatic encephalopathy through effects on systemic inflammation. Cirrhosis is associated with increased intestinal permeability and bacterial translocation, allowing microbial products to enter the portal and systemic circulation. These products activate innate immune pathways and stimulate inflammatory cytokine production. Inflammation can enhance the neurological effects of ammonia by promoting oxidative stress, altering astrocyte function, and increasing cerebral vulnerability. Stadlbauer et al. found that probiotic administration improved neutrophil phagocytic capacity and modified cytokine and toll-like receptor responses in patients with compensated alcoholic cirrhosis [21]. Although that study was small and focused primarily on immune function, its findings provide mechanistic support for the possibility that probiotics may reduce the inflammatory component of hepatic encephalopathy.

Probiotics have also been compared with other ammonia-lowering therapies. Sharma et al. reported that probiotics, rifaximin, and L-ornithine L-aspartate were each more effective than placebo in reversing minimal hepatic encephalopathy [22]. These findings indicate that interventions acting through different pathways may produce similar improvements in cognitive performance. Probiotics may therefore be most appropriately considered an adjunctive treatment rather than a universal replacement for lactulose or rifaximin. Their potential advantages include generally favourable tolerability, ease of administration, and a lower likelihood of diarrhoea, abdominal discomfort, or altered taste compared with some conventional therapies. Nevertheless, probiotic effects are strain-specific, and the benefits of one formulation cannot automatically be generalized to all commercially available products.

Recent pooled evidence further supports the results of the present study. A 2024 meta-analysis reported that probiotic therapy improved blood ammonia levels, cognitive function, liver-related parameters, and remission of minimal hepatic encephalopathy [23]. However, the authors also identified substantial variation among studies in probiotic strains, dosages, treatment durations, diagnostic criteria, participant characteristics, and control interventions. Such heterogeneity limits the ability to define an optimal probiotic preparation or standardized treatment duration.

The findings of the present study should therefore be interpreted in light of several limitations. The four-week intervention period was relatively short and may not reflect long-term recurrence, hospitalization, quality of life, or survival outcomes. Because probiotics were provided alongside standard management, the individual contribution of probiotic therapy is difficult to isolate. Serum ammonia is influenced by sample collection, processing, renal function, recent food intake, gastrointestinal bleeding, muscle mass, and other clinical factors. Future randomized, double-blind, placebo-controlled studies should include larger samples, clearly identified probiotic strains, standardized doses, longer follow-up, validated cognitive assessments, inflammatory and microbiome markers, adverse-event monitoring, and clinically meaningful outcomes. Overall, the present findings suggest that probiotics may offer a safe and useful supportive approach for improving neurological status and reducing serum ammonia in patients with hepatic encephalopathy.

CONCLUSION

The findings of this study demonstrate that probiotic therapy plays a significant role in improving clinical outcomes in patients suffering from Hepatic Encephalopathy. The administration of probiotics along with standard treatment resulted in noticeable improvement in clinical grading of encephalopathy as well as a significant reduction in serum ammonia levels. Since elevated ammonia is a major contributor to the neurological manifestations associated with hepatic encephalopathy, lowering its concentration can lead to meaningful improvement in cognitive function, mental status, and overall neurological health. These results indicate that targeting the intestinal microbiota may be an important therapeutic strategy in the management of this condition.

The beneficial effects of Probiotics are largely attributed to their ability to restore the balance of intestinal flora, reduce the population of ammonia-producing bacteria, and enhance intestinal barrier integrity. By improving gut microbial composition and reducing intestinal permeability, probiotics help limit the absorption of harmful toxins into the bloodstream. This mechanism reduces the toxic burden on the brain and supports improved neurological function. Furthermore, probiotics may exert anti-inflammatory effects that help decrease systemic inflammation commonly observed in patients with advanced liver disease.

Another important implication of this study is that probiotic therapy can serve as a useful adjunct to conventional treatments such as lactulose and other supportive measures. Standard therapies primarily focus on decreasing ammonia production and improving its elimination; however, probiotics address the underlying disturbance in gut microbiota that contributes to toxin generation. Because probiotics are generally safe, well tolerated, and relatively inexpensive, they represent a practical option for long-term management and prevention of recurrent episodes of hepatic encephalopathy, particularly in patients with underlying conditions such as Liver Cirrhosis.

In conclusion, the results of this study support the incorporation of probiotic therapy as a complementary approach in the treatment of hepatic encephalopathy. By improving both clinical symptoms and biochemical parameters, probiotics may help enhance patient quality of life and reduce the burden of disease. Nevertheless, further large-scale randomized controlled trials with longer follow-up periods are recommended to confirm these findings and to establish standardized guidelines regarding the optimal strains, dosage, and duration of probiotic therapy in the management of hepatic encephalopathy.

Recommendations

Based on the findings of this study, probiotics may be considered as a supportive adjunct to standard medical therapy for patients with hepatic encephalopathy, particularly for improving clinical symptoms and reducing serum ammonia levels. Healthcare professionals should select well-characterized probiotic strains, monitor treatment response, and continue established therapies such as lactulose or rifaximin according to clinical indications. Patient education should

emphasize medication adherence, dietary management, prevention of constipation, early recognition of precipitating factors, and regular follow-up. Future research should involve larger randomized controlled trials with longer follow-up periods to evaluate recurrence, hospitalization, quality of life, safety, and mortality outcomes. Studies should also compare different probiotic strains, doses, and treatment durations to identify the most effective regimen and develop standardized clinical guidelines for the use of probiotics in hepatic encephalopathy.

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