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AN INTERVENTIONAL STUDY ON THE EFFICACY OF RIFAXIMIN-LACTULOSE COMBINATION WITH AND WITHOUT PROBIOTICS IN THE TREATMENT OF HEPATIC ENCEPHALOPATHY IN SOUTH KERALA

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ABSTRACT: Background: Hepatic Encephalopathy (HE) is a condition that is generally seen in individuals suffering from liver cirrhosis. HE is described as a range of neuropsychiatric diseases in individuals with liver diseases. It is characterized by personality changes, intellectual impairment and a depressed consciousness. Toxic substances that are generally excluded from the body by the liver accumulate in the blood and ultimately reach the brain, causing HE. Incidence rate of HE is estimated by various authors at about 30-84% of cases with liver cirrhosis depending on the applied diagnostic methods and examined population. Ammonia is one of the major neurotoxins produced in HE. Various triggers of HE includes renal failure, GI bleeding, constipation, infection, alcohol consumption, etc. Typically, bacteria within the gastrointestinal tract generate ammonia, which is then processed and eliminated by the liver through metabolism. But in HE there is either a drop in the number of the performing hepatocytes, portosystemic shunting or both, resulting in dropped ammonia clearance and hyperammonaemia. Once ammonia crosses BBB, it has multiple neurotoxic effects, and which ultimately results in symptoms of HE. Earlier approaches towards the treatment of HE included antibiotics, lactulose, zinc supplementation etc. In today's scenario probiotics have also been added to this regimen, contributing to reduction in ammonia levels. Hence improving the symptoms of HE.

INTRODUCTION: Hepatic encephalopathy (HE) is a complex and serious neurological condition that arises as a consequence of liver dysfunction, particularly in cases of advanced liver disease ¹. However, when the liver is impaired due to conditions such as cirrhosis, hepatitis, or liver failure, harmful substances, primarily ammonia, accumulate in the bloodstream and eventually affect the brain.

The condition is marked by alterations in mood, personality changes, confusion, and in severe cases, coma ². HE is often categorized into two types: overt HE, characterized by noticeable and significant neurological symptoms, and covert HE, which involves more subtle cognitive changes that may not be immediately apparent ^{3,4}.

The precise mechanisms underlying HE are multifactorial, involving the toxic effects of elevated ammonia levels, inflammation, and the disruption of neurotransmitter balance in the brain. Ammonia, a byproduct of protein metabolism normally detoxified by the liver, becomes neurotoxic when its clearance is compromised ⁵. This toxic build-up disrupts neurotransmission,

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leading to the neurological symptoms observed in HE. Hepatic encephalopathy can manifest in various ways, including confusion, forgetfulness, personality changes, slurred speech, and impaired coordination^{6, 7}. In severe cases, it can cause coma or even death. Other symptoms may include jaundice, hand tremors and difficulty with fine motor skills. It is diagnosed by Clinical Evaluation, Laboratory Tests (LFT, serum ammonia, CBC, electrolyte levels and arterial blood gases), Imaging Studies (MRI, CT scans), Neuropsychological Assessments and Additional Diagnostic Procedures (liver biopsy, EEG, SPECT)^{8, 9}. The combination of Rifaximin and Lactulose is often considered to have a synergistic effect in managing Hepatic Encephalopathy^{10, 11}. While Rifaximin acts to reduce ammonia production in the gut, lactulose works to trap ammonia and eliminate it through bowel movements^{12, 13, 14}. Studies have shown that the combination of rifaximin and lactulose is effective in managing hepatic encephalopathy by reducing ammonia levels and improving symptoms^{15, 16, 17, 18}. The addition of probiotics to the rifaximin and lactulose regimen may provide additional benefits by promoting a healthier gut microbiota^{19, 20}. Probiotics may contribute to the stability and diversity of the gut flora. The combination with probiotics may enhance patient tolerance by potentially reducing side effects associated with antibiotic use²¹.

MATERIALS AND METHODS: The study was conducted among Hepatic encephalopathy patients under Gastroenterology department at NIMS Medicity, Neyyattinkara, Tertiary care Teaching hospital in Thiruvananthapuram. The sample size at 95% confidence interval was 52 with a level of significance of 0.05. The study was sanctioned by Institutional Ethical Committee with Approval number: NIMS/IEC/2023/09. The p-Value was determined by using Shapiro-Wilk test and Friedman test. After the collection of the data, it was recorded and analysed using MS Excel spreadsheet and SPSS version R.

Experimental Design: The study was a prospective interventional approach which was carried out over a period of 6 months commencing from September 2023 to February 2024. The study included the patients above 30 years and below 80 years. In-patients and Out-patients, Hepatic

Encephalopathy patients with comorbid conditions and excluded those patients who are pregnant and lactating women, has a known case of cancer and autoimmune disease patients in Intensive-Care-Units and patients on treatment with Rifaximin/Lactulose/Probiotics for other condition.

Study Variables: Patient demographic details and clinical characteristic details (laboratory parameters) and patient specific comorbidities.

Data Collection and Analysis: All the relevant data was collected in a structured data collection form and using specific assessment scales. The data was collected and submitted to proper statistical analysis. Data were obtained in a systematic manner utilizing a data collection form. The data was collected from both inpatient and outpatient with Hepatic Encephalopathy and have the same for more than one year. Information regarding the study (patient demographics, reason for admission, medication history) was collected by interviewing the patients, and patient caregivers. The Child-Turcotte-Pugh score was used to analyze the extend of liver impairment based on the presence of ascites and other LFT values. The quality of life of patient was assessed using the Chronic Liver Disease Questionnaire that assessed the patient condition based on 6 domains: abdominal symptoms, fatigue, systemic symptoms, activity, emotional function and worry. After the collection of data, it was recorded and analyzed using an MS Excel spreadsheet.

Tools and Questionnaires used: Data collection form is a way of recording approach to obtaining the data that are needed to perform the analysis.

- AASLD Guidelines: the clinical practice guidelines for diagnosis and management of Hepatic Encephalopathy.
- CTP Score: CTP score stands for Child-Turcotte-Pugh score that is used to assess the severity of cirrhosis based on the presence of ascites.
- CLDQ: it is a questionnaire that evaluates 6 domains: abdominal symptoms, fatigue, systemic symptoms, activity, emotional function and worry.

RESULTS AND DISCUSSION:

The study population was allocated into two groups as follows:

Group A: Treatment with Rifaximin-Lactulose

Total number of patients: 24

Group B: Treatment with Rifaximin-Lactulose + Probiotics

Total number of patients: 23

Drop Out:

Total number of patients: 2

Group A: 1 patient

Group B: 1 patient

Age-Wise Distribution: The table summarizes the descriptive results according to age of patients; majority of individuals were in the age group of 46 - 75 years. From 47 patients, 36 (76.594%) patients belong to the age group of 46-75 years, followed by an age group of above 76 years, that is 7 (14.893%) from 47 HE patients.

TABLE 1: AGE-WISE DISTRIBUTION

Variable	Frequency (N)	Percentage (%)
30-45	4	8.510
46-60	18	38.297
61-75	18	38.297
ABOVE 76	7	14.893

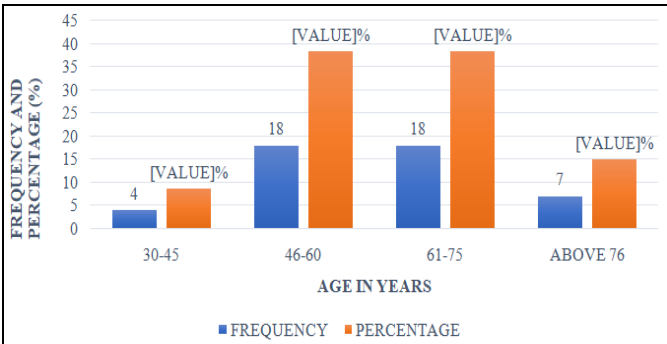


FIG. 1: AGE-WISE DISTRIBUTION

Gender-Wise Distribution: The table summarizes the prevalence of HE occurrence with gender. Out of 47 patients, 37(78.72%) patients are males and

10 (21.27%) patients are females. This indicates that gender influences the prevalence; however, we had greater number of males than females in the study.

TABLE 2: GENDER-WISE DISTRIBUTION

Gender	Frequency (N)	Percentage (%)
Male	37	78.72
Female	10	21.27
Total	47	100

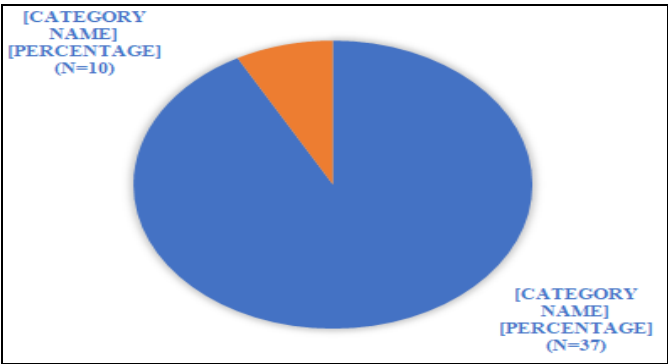


FIG. 2: GENDER-WISE DISTRIBUTION

Distribution of Social History: Alcoholism has been found to be a major contributing factor to the disease condition in this study population. Among 37 males in the study population, 21 (90%) patients were found to have a social history of alcoholism. Smoking was another contributing factor which accounted for 4% of the males in study population.

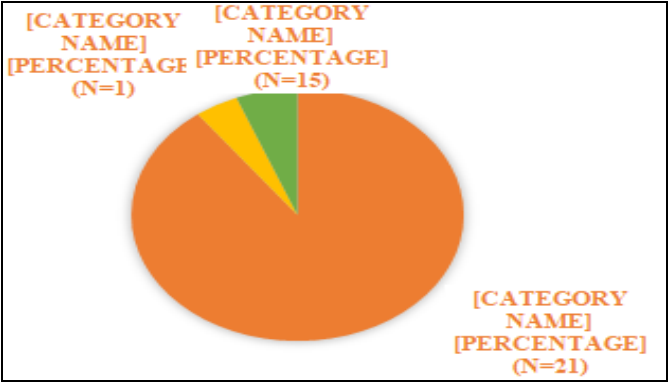


FIG. 3: DISTRIBUTION OF SOCIAL HISTORY

Correlation between Ammonia and CLDQ: The table summarizes that there is a minimal correlation between ammonia and CLDQ score with p value of 0.00. At some point the values of ammonia and CLDQ scores may intersect resulting in a correlation between the two parameters.

TABLE 3: CORRELATION BETWEEN AMMONIA AND CLDQ

Parameter 1	Parameter 2	r	p	Method
Ammonia	CLDQ	0.086	0.689	Pearson Correlation

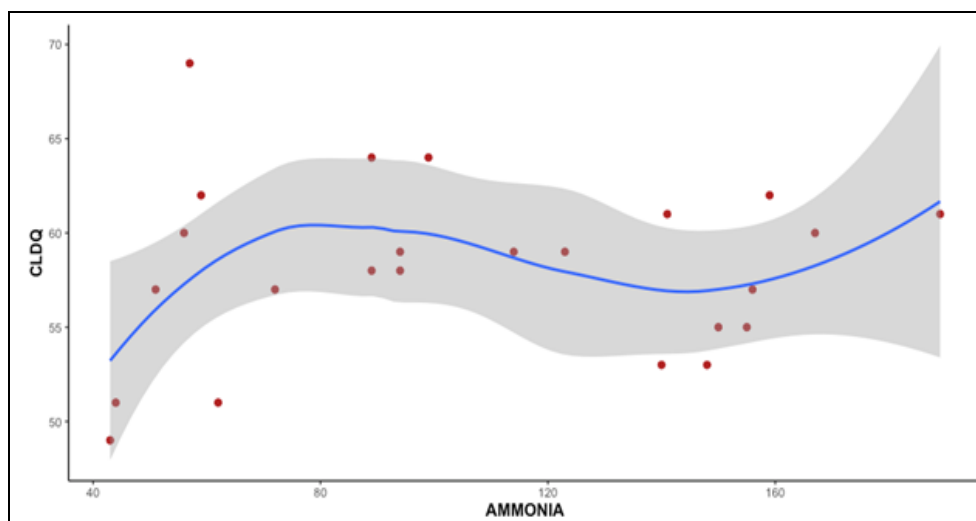


FIG. 4: CORRELATION BETWEEN AMMONIA AND CLDQ

Child-Turcotte-Pugh Score Distribution: The Figure showed an improvement in the Child-Turcotte-Pugh score although the classes remained the same. By the end of the second follow up both

the groups showed a significant improvement in relation to the Child-Turcotte-Pugh score, but a significant improvement was not contributed by the Probiotics in the said duration.

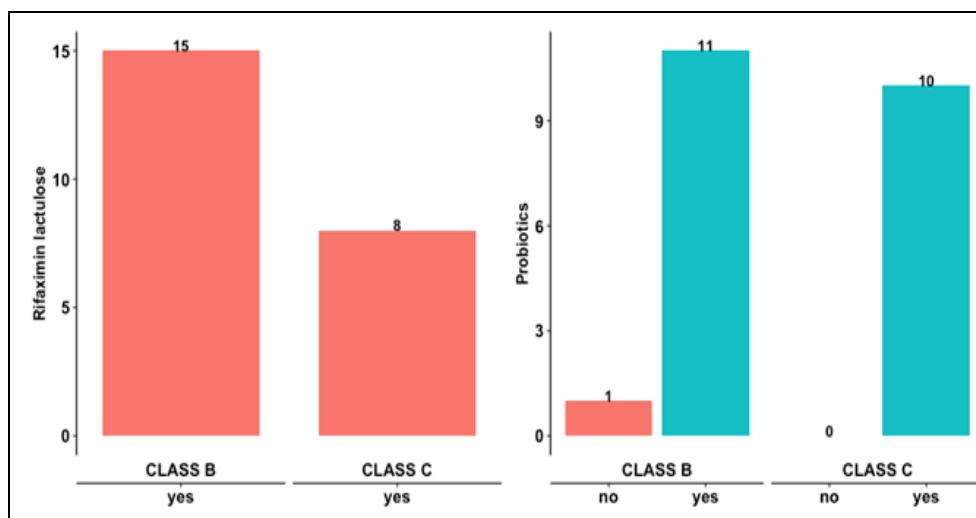


FIG. 5: CHILD-TURCOTTE-PUGH SCORE DISTRIBUTION

CONCLUSION: In the year 2023-2024, a prospective observational study was done in patients with Hepatic Encephalopathy under the supervision of the Gastroenterology Department for a duration of six months. Demographic details, Laboratory parameters in relation to the condition, the status of liver using Child-Turcotte-Pugh score and quality of life of patients using CLDQ were assessed during the course of the study. Out of 47 patients, most of the patients were males and the most prominent age group was 46-75 years. Among males, alcoholism has shown to be the major contributing factor to the occurrence of the condition. The average change in Child-Pugh-Score

was found to be 4.07 ± 1.64 in group A and 3.36 ± 1.40 in group B. The study summarizes that there is a minimal correlation between ammonia and CLDQ score with a p value of 0.00. At some point the values of ammonia and CLDQ scores may intersect resulting in correlation between the two parameters.

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CONFLICT OF INTEREST: The authors declare that they have no conflict of interest.

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