

ORIGINAL ARTICLE

Incidence of Hepatic Encephalopathy in Patients with Spontaneous Bacterial Peritonitis Using Rifaximin and Lactulose: A Study at a Tertiary Care Hospital in RawalpindiMuhammad Saad Aziz^{1*}, Fuad Ahmad Siddiqi¹, Muhammad Hammad¹, Wasif Anwar², Sidra Aman³**ABSTRACT**

Objective: To determine the incidence of hepatic encephalopathy (HE) in cirrhosis patients with spontaneous bacterial peritonitis receiving Lactulose, Rifaximin, or a combination of both, and to compare the efficacy of these treatments.

Study Design: Cross-sectional study.

Place and Duration of Study: The study was conducted at the Department of Medicine, Pak Emirates Military Hospital Rawalpindi, Pakistan, from September 2021 to August 2022.

Methods: Using consecutive sampling, diagnosed cases of decompensated Chronic Liver Disease with clinically apparent ascites, visiting the outpatient department, with or without signs and symptoms of spontaneous bacterial peritonitis (SBP) were included in the study after laboratory confirmation of spontaneous bacterial peritonitis. The drug history was taken, and hepatic encephalopathy was diagnosed using Mini-mental Scale Examination and West-Haven criteria. The incidence of hepatic encephalopathy was compared across the groups using the Pearson Chi-square test.

Results: A total of 60 diagnosed Chronic liver disease patients with spontaneous bacterial peritonitis were included in the study. Rifaximin was being used by 41.7% (n=25), 41.7% (n=25) patients were using lactulose alone and 16.7% (n=10) were using a combination of both drugs. 58.3% (n=35) of patients were found to have hepatic encephalopathy. Out of these, 42.8% (n=15) were using rifaximin alone, 54.2% (n=19) were using lactulose alone, while just 2% (n=1) patients were using the combination of both drugs ($P < 0.001$).

Conclusion: Spontaneous Bacterial Peritonitis is an important trigger of hepatic encephalopathy in the setting of decompensated chronic liver disease and is associated with high mortality. The use of lactulose and rifaximin combination is superior to monotherapy with either of them for preventing hepatic encephalopathy in these patients.

Keywords: Ascites, Decompensated Chronic Liver Disease, Hepatic Encephalopathy, Lactulose, Rifaximin, Spontaneous Bacterial Peritonitis.

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Introduction

Portosystemic or hepatic encephalopathy (HE) is a serious and life-threatening complication of chronic liver disease that manifests as disturbance of consciousness, abnormal behavior, and coma.¹ HE alone is an independent predictor of mortality and is associated with a poor outcome. Even in its subclinical form, HE negatively impacts patients' functional status and quality of life of patients and

their caregivers.²

HE is an underestimated problem. It should be considered a common complication of liver failure, which can present as a hyperacute, acute, subacute, or chronic state. It is precipitated by several triggers including infections, variceal bleeding, constipation, drugs, surgery, or portosystemic shunting.³ The altered state of consciousness in HE has been attributed to an inflammatory response to injury and glutamine replacing glutamate which is the normal neurotransmitter.⁴ Glutamate decreases the speed of normal neurotransmission in the brain. Some authors have also implicated GABA channels in the pathogenesis of HE.⁵ Hepatic encephalopathy can occur in the setting of acute liver failure, portosystemic shunting in the absence of liver function, or due to cirrhosis.⁶

The severity of HE has been classically graded as per West Haven Criteria in Grades I through IV. However, the reliability of this grading has been questioned in the recent decade and has led to the addition of a separate grade known as minimal HE or MHE. Grade I HE and MHE are often combined and referred to as overt HE. Altered sleep rhythm and confusion make upgrade 2 HE, whereas stupor and unresponsiveness mean grades 3 and 4 HE, respectively.⁶ Lactulose is considered the first-line treatment option for patients with HE. It reduces the concentration of ammonia-producing substrates in the intestinal lumen and pH in the colon by producing organic acids by bacterial fermentation and acting as an osmotic purgative.⁷ Rifaximin, a non-absorbable antibiotic, was approved for the prevention and treatment of HE by the US Food and Drug Administration in 2010.⁸ Rifaximin should be used in combination with lactulose for patients with HE.⁹ Patients with overt or grade 1 / 2 HE are treated with oral lactulose. Those who have grade 3 / 4 HE must be managed in an ICU and may require lactulose 30% enema as well. Following an episode of HE, the use of lactulose has been strongly recommended for prophylaxis by the European Association for the Study of Liver. For patients who have experienced more than one episode of HE in the last 6 months, rifaximin has been advocated as an adjunct to lactulose for prophylaxis.¹⁰ An important aspect of treating HE is addressing the underlying trigger. SBP is an

important trigger for decompensation of liver function in CLD which may manifest as HE. SBP occurs because of gut microbiota translocating into the peritoneal cavity. Bacteria traverse the intestinal wall and colonize the mesenteric nodes. Urease-producing bacteria such as *E. coli* and *Klebsiella*, have been implicated in the genesis of HE in SBP.¹¹ Diuretic therapy, prophylactic antibiotics, and restricting the use of proton pump inhibitors are recommended for the prevention of SBP.

The use of rifaximin and lactulose alone or in combination for the prevention of HE has been a bone of contention amongst clinicians in the past decade. Towards the end of the decade, the entire evidence from randomized control trials was reviewed and the combination is superior to either agent alone. Our study set out to establish this very fact in the subset of these patients having spontaneous bacterial peritonitis as the underlying trigger.

Methods

This study was conducted at the Medicine Department of the Pak Emirates Military Hospital (PEMH) Rawalpindi, Pakistan from September 2021 to August 2022. Sample size was calculated using the WHO sample size calculator keeping in view the reported prevalence of SBP in cirrhosis patients presenting in the outpatient department as 4%. It came out to be 60.¹² Permission was sought from the Pak Emirates Military Hospital Ethical Review Committee vide A/28/Med/261/2021 for this study. A thorough informed consent was taken from the patients who were enrolled in the study.

Inclusion Criteria included diagnosed cases of decompensated chronic liver disease visiting the outpatient department of Pak Emirates Military Hospital, Rawalpindi with or without signs and symptoms suggestive of SBP but having clinically apparent ascites. SBP, whether symptomatic or asymptomatic was confirmed via diagnostic ascitic tap indicated by a cell count of more than 250 cell/cmm.

Exclusion Criteria excluded patients of cirrhosis without clinically apparent ascites and clinical or laboratory evidence of SBP upon diagnostic ascitic tap.

All included patients were subjected to diagnostic

ascitic tap on an outdoor/indoor basis and results were followed up. Using a sterilized technique, a diagnostic ascitic tap was performed by the resident in the outpatient department of the ward. The collected ascitic fluid sample was sent to the hospital laboratory for Fluid routine examination. The results of which were collected after 2 hours from the laboratory. At the time of the ascitic tap, drug history with regards to the use of rifaximin and lactulose and any prior episode of HE was recorded. Assessment for HE was performed using a mini-mental scale examination. A score below 27.5 was considered to have minimal/overt HE whereas the rest of the grading was done as per the West Haven Criteria.¹³ Data were entered in the statistical package for social sciences (SPSS) software version 23.00 and analyzed. Mean and standard deviation was calculated for age whereas frequencies were calculated for the rest of the variables. The incidence of HE across the groups was compared using the Pearson Chi-square test and a *P-value* of <0.05 was considered significant.

Results

A total of 60 patients were enrolled in the study after fulfilling the inclusion criteria. They had an age of 55.9 ± 12.4 years. Out of these, 58.3% (n=35) were males and 41.7% (n=25) were females. The decompensated liver disease was caused by Hepatitis C in 55% (n=33) of patients, Hepatitis B in 36.7% (n=22), and non-alcoholic fatty liver disease (NAFLD) in 8.3% (n=5) patients (Figure.1).

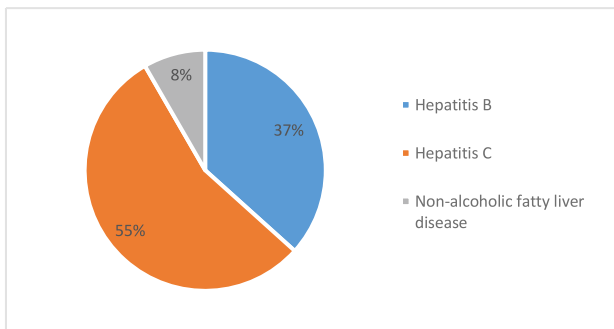


Fig.1: Causes of decompensated chronic liver disease (n=60)

All patients were confirmed as having SBP via ascitic fluid routine examination showing a cell count of more than 250 cells/cmm. At the time of enrollment in the study, 50% (n=30) had symptoms of SBP for less than 5 days, 26.7% (n=16) had symptoms for 5-

10 days and 23.3% (n=14) had symptoms for more than 10 days. Fever was reported by 76.7% (n=46) patients, while 81.7% (n=49) complained of abdominal pain. Out of the 60 patients, only 10% (n=6) patients were asymptomatic. Fever as well as abdominal pain was reported by 68.3% (n=41), while 13.3%(n=8) had abdominal pain in isolation and 8.3% (n=5) had fever alone. Grade 2 ascites were seen in 75% (n=45) patients while 25% (n=15) had grade 3 ascites.

With regards to medication, 41.7% (n=25) patients were using rifaximin alone, 41.7% (n=25) were using lactulose alone and 16.7% (n=10) were using a combination of both drugs. Overt or a higher grade HE was found in 58.3% (n=35) patients. Out of these 35 patients, 42.8% (n=15) were using rifaximin alone, 54.2% (n=19) were using lactulose alone while just 2% (n=1) patients were using the combination of both drugs (*P* = 0.001) (Figure.2).

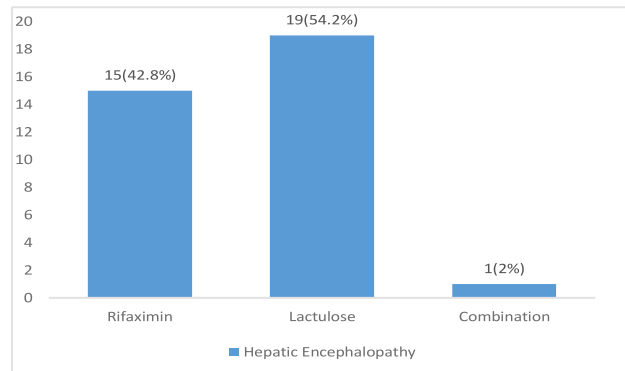


Fig.2: Hepatic encephalopathy in spontaneous bacterial peritonitis patients using rifaximin and lactulose alone or in combination (n=60)

The grade of HE was also compared against the use of a single agent versus combination. Out of 15 patients with HE in the rifaximin, 46.6% (n=7) had Overt HE, 46.6% (n=7) had grade 2 HE and only 6% (n=1) had grade 3 HE. In the lactulose group, 31.5% (n=6) had overt HE, 36.8% (n=7) had grade 2 HE, 26.3% (n=5) had grade 3 HE while 5% (n=1) had grade 4 HE. In the combination group with HE, only one individual had overt HE (Figure.3).

HE was not found in 41.7% (n=25) patients. Out of these, 40% (n=10) were using rifaximin only, 24% (n=6) were using lactulose only whereas 36% (n=9) were using the combination of both drugs.

Discussion

Our study included cirrhosis patients belonging to all

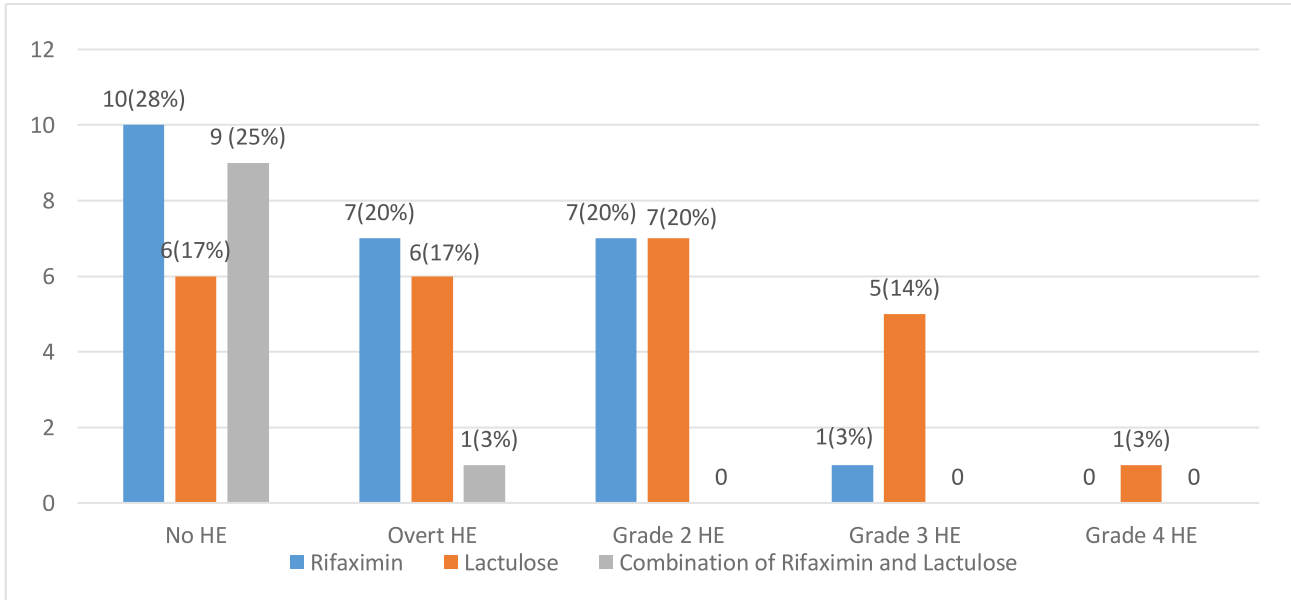


Fig. 3: Comparison of grades of Hepatic Encephalopathy (HE) against use of single agent versus combination (P = 0.009)

age groups and both genders, but the mean was 55 years which is higher than what is routinely seen in a society where alcoholism is not abhorred on religious grounds. The predominant cause of cirrhosis in our country is chronic hepatitis secondary to hepatitis B or C virus infections which have over the past few decades become rampant. The unhygienic practices of barbers, quacks, and dental care setups have been largely the cause of this. The major presenting symptoms of SBP noted in our study were fever and abdominal pain, with a prevalence even higher than has been reported in the literature especially when subclinical cases are also probed retrospectively. Over 50% of the cases of SBP were found to be having HE of some grade in our study. As far as the main objective of this study is concerned, we demonstrated and thus replicated the fact that the combination of rifaximin and lactulose is superior to either of the drugs alone in preventing the development of HE in patients having clinical or subclinical SBP. Patients who were receiving rifaximin alone also had less incidence of HEs compared to lactulose. Most of the patients in our study had overt HE, representing an underestimation of the problem. This implies that the importance of routinely carrying out Mini-Mental State Examination (MMSE) in CLD patients in the outpatient department ought not to be disregarded as it certainly helps predict the course of

their illness and timely intervention.

A relatively lower mean age has been reported in our neighboring country by Praharaj DL et al. in a randomized controlled trial that compared Norfloxacin to rifaximin for the prevention of SBP.¹⁴ In another Indian-based study conducted by Paul K et al. most of the patients of cirrhosis were male owing to alcoholism as the underlying cause which is in contrast to our study, where Hepatitis B or C were the leading causes of cirrhosis.¹⁵ Hepatitis C has become the leading cause of chronic liver disease in Pakistan as per the latest statistics. Pakistan has the second largest burden of the disease globally as per Abbas Z et al. It has been documented in the literature by Koulaouzidis A et al. that around 68% of the patients have a fever while we reported a slightly higher percentage.¹⁶ Abdominal pain, which has been reported in around 50% of SBP patients was 30% less as compared to reported in our study. The incidence of reported HE is, however, comparable.¹⁷ Oliver et al have reported that the use of a combination of rifaximin and lactulose is superior to either agent alone in preventing HE generally by any cause.¹⁸ EASL guidelines also recommend the use of a combination instead of a single agent.¹⁰

The role of rifaximin has been advocated for secondary prevention of SBP by Praharaj DL et al. Although in randomized controlled trials, rifaximin is not superior to lactulose in contrast to our findings

and both are deemed equally effective in the prevention of HE, rifaximin has an advantage of better tolerability over lactulose.¹⁴ The combination of these two drugs has been shown to be superior to either agent alone by Maharshi S et al. The better tolerability of rifaximin by the patients and a smaller sample size may be the reason, that we were unable to replicate this result.¹⁹

For detecting overt HE, the MMSE is a lengthy examination and consumes time. The use of a different scale such as Abbreviated Mental Test Score (AMTS) may be useful in these settings because HE is an independent predictor of mortality in patients with liver failure. Verma N et al. have reported that the incidence of mortality increases with the grade of HE.²⁰ The authors of the study are aware of its limitations. This study was conducted in a single center in Pakistan that caters to healthcare for a specific clientele. The findings of this study cannot be generalized to the entire population. The sample size of our study is also very small because of time constraints, lack of funding, and the limited number of patients with complaints under consideration visiting the hospital. Larger, multicenter trials are needed to explore the efficacy and safety of the treatment on a broader scale.

Conclusion

Spontaneous Bacterial Peritonitis is a very important trigger of hepatic encephalopathy in the presence of portal hypertension. They are associated with high mortality during illness as well as in the short term and long term. Prevention of HE with lactulose and rifaximin combination is a cost-effective treatment for the patients. Further to this, rifaximin may also have a role in the prevention of SBP.

Use of both rifaximin and lactulose in combination is superior to either one of them being used alone, in the prevention of HE in patients with decompensated chronic liver disease and SBP.

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Conflict of Interest: The authors declare no conflict of interest

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Authors Contribution

MSA: Idea conception, study designing, data collection, data analysis, results and interpretation, manuscript writing and proofreading

FAS: Idea conception, study designing, manuscript writing and proofreading

MH: Data collection, data analysis, results and interpretation, manuscript writing and proofreading

WA: Study designing, data analysis, results and interpretation, manuscript writing and proofreading

SA: Data collection, data analysis, results and interpretation

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