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ORIGINAL ARTICLE

Frequency of Recurrence of Hepatic Encephalopathy in Patients of Chronic Liver Disease Treated With Rifaximin

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ABSTRACT

Aim: To determine the frequency of recurrence of hepatic encephalopathy in patients treated with Rifaximin.
Study design: Observational cross-sectional study.
Setting & duration: Department of Medicine, Services institute of Medical Sciences Lahore for duration of 12 months.
Methodology: Hepatic encephalopathy was diagnosed using West-Haven classification in patients of chronic liver disease. Recurrence was considered if a new episode of hepatic encephalopathy occurred within 3 months after initiation of treatment. A total 120 patients of chronic liver disease having had an episode of recent hepatic encephalopathy within the last 3 months, of both genders, above 20 years of age with hepatic encephalopathy were included in the study. The patients were followed for 3 months after initiation of therapy and any episode of recurrence of hepatic encephalopathy was recorded.
Results: Mean age was 51.5±12.2 years and 52.3±12.8 years respectively in Rifaximin and Placebo groups. Fourteen (23.3%) patients in Rifaximin group and 17(28.3%) in placebo group were younger than 40 years of age. Thirty-three (55%) patients in Rifaximin group were male versus 29(48.3%) patients in Placebo group. Fifteen (25%) patients in Rifaximin Group developed hepatic encephalopathy by 3 months of follow up as compared to 31(51.7%) patients in Placebo Group
Conclusion: Frequency of recurrence of hepatic encephalopathy is significantly lower in Rifaximin treated patients.
Keywords: Hepatic Encephalopathy, Recurrence, Rifaximin.

INTRODUCTION

Hepatic encephalopathy (HE) is not an uncommon complication of liver cirrhosis[1]. Hepatic encephalopathy may be seen in up to 50% of patients of chronic liver disease admitted to the hospital.[2] Development of hepatic encephalopathy seems unrelated to underlying etiology of liver cirrhosis.[3] However increasing severity and frequency of HE episodes increase mortality risk.[4] The clinical features of Hepatic Encephaloathy encompass altered behavior to diminished mental conscious status to deep coma[5]. The diagnosis of overt hepatic encephalopathy relies on impaired mental status classified by West-Haven criteria and neuro-psychiatric dysfunction[6]. It has been postulated that HE is caused by systemic accumulation of certain GIT-derived neurotoxins especially hyperammonemia in patients with hepatic dysfunction and increased porto-systemic blood shunting[4,5]. Therefore the treatment therapies in HE rely on reducing the neurotoxin and nitrogenous load from the gastro-intestinal track.

Rifaximin is an oral antimicrobial which is minimally absorbed from the gut and has a broad spectrum of action against anaerobes, gram-negative and gram-positive enteric bacteria with low risk of resistance[7]. Bass et al[8] who reported recurrence of HE in 22.1% of patients treated with rifaximin versus 45.9% in placebo group. Larsen et al[9] reported rifaximin to be effective and safe in treatment of hepatic encephalopathy. In treatment of hepatic encephalopathy, Butt el al[10] demonstrated improvement in 67.6% patients treated with Rifaximin as compared to 58.4% in patients without rifaximin.

The rationale of present study was to find out the frequency of recurrence of hepatic encephalopathy in patients of chronic liver disease treated with rifixamin, so that appropriate adjustment to therapy may be made in such patients to reduce disease burden, morbidity and mortality.

METHODS

The observational cross-sectional study was conducted at Department of Medicine, Services institute of Medical Sciences Lahore for duration of 12 months to determine the frequency of recurrence of hepatic encephalopathy in patients treated with rifaximin. Hepatic encephalopathy was diagnosed using West-Haven classification in patients of chronic liver disease. Recurrence was considered if a new episode of hepatic encephalopathy occurred within 3 months after initiation of treatment. Using WHO calculator, sample size of 120 patients was calculated keeping margin of error 5% and confidence interval 95%. Using non-probability purposive sampling technique, 120 patients of chronic liver disease having had an episode of recent hepatic encephalopathy within the last 3 months, of both genders, above 20 years of age with hepatic encephalopathy were included in the study. Patients having acute hepatic failure, acute or chronic renal failure, diabetes mellitus, hepatic or any other malignancy and pregnancy as determined by medical history and detailed clinical examination were excluded from the study.

After taking informed consent, patients were segregated into 2 groups (Rifaximin Versus Placebo) by lottery method. All patients were given standard treatment as per hospital protocol. Rifaximin was given 550mg twice daily. The patients were followed for 3 months after initiation of therapy and any episode of recurrence of hepatic encephalopathy was recorded. Data was entered and analyzed using SPSS version 21.0. Quantitative variables were measured by mean and standard deviation. Frequency and percentages were calculated for qualitative variables. Chi-square test with p-value <0.05 as significant was applied for stratification.

RESULTS

In the present study, a total of 120 cases (60 in each group) of chronic liver disease were enrolled to determine the frequency of recurrence of hepatic encephalopathy in patients treated with rifaximin. Mean age of the patients was 51.9±12.5 years. Sixty-two (51.7%) were male and 58(48.3%) were female. Recurrence of hepatic encephalopathy was seen in 46 (38.6%) patients of chronic liver disease by 3 months of follow up. With regards to the 2 groups, mean age was 51.5±12.2 years and 52.3±12.8 years respectively in Rifaximin and Placebo groups. Fourteen (23.3%) patients in Rifaximin group and 17(28.3%) in placebo group were younger than 40 years of age as shown in Table 1. Forty-six (76.6%) patients in Rifaximin Group were aged older than 40 years as compared to 43(71.6%) in Placebo Group as shown in Table 1. Thirty-three (55%) patients in Rifaximin group and 29(48.3%) patients in Placebo group were male as shown in Table 1. Twenty-

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seven (45.0%) patients in the Rifaximin group were female as opposed to 31(51.7%) in placebo group as shown in Table 1. Fifteen (25%) patients in Rifaximin Group developed hepatic encephalopathy by 3 months of follow up as compared to 31(51.7%) patients in Placebo Group, demonstrating a statistically significant association (p-value 0.002) as shown in Table 2. Stratification of age and gender with regards to treatment group assigned in patients who developed a recurrence of hepatic encephalopathy is shown in Table 3 and Table 4 respectively.

Table 1: Comparison of demographic variables according to Treatment Group Assigned

Demographic variables	Rifaximin Group	Placebo Group
Mean Age	51.5±12.2 years	52.3±12.8 years
Mean Age	51.5±12.2 years	52.3±12.8 years
Age groups		
Less than 40 years	14 (23.3%)	17 (28.3%)
More than 40 years	46 (76.6%)	43 (71.6%)
Gender		
Male	33 (55.0%)	29 (48.3%)
Female	27 (45.0%)	31 (51.7%)

Table 2: Recurrence of Hepatic Encephalopathy according to Treatment Group Assigned

Recurrence of Hepatic Encephalopathy	Rifaximin Group	Placebo Group
Present	15 (25.0%)	31 (51.7%)
Absent	45 (45.0%)	29 (48.3%)
Total	60	60

P value 0.002 (significant)

Table 3: Stratification of Age with regards to Treatment Group Assigned in patients with recurrence of Hepatic Encephalopathy

Age (years)	Rifaximin Group	Placebo Group
Less than 40	6 (40.0%)	11 (35.5%)
More than 40	9 (60.0%)	20 (64.5%)
Total	15	31

P value 0.671 (non significant)

Table 4: Stratification of Gender with regards to Treatment Group Assigned in patients with recurrence of Hepatic Encephalopathy

Gender	Rifaximin Group	Placebo Group
Male	8 (53.3%)	18 (58.1%)
Female	7 (46.7%)	13 (41.9%)
Total	15	31

P value0.903 (non significant)

DISCUSSION

Hepatic encephalopathy (HE) is not an uncommon complication of liver cirrhosis. Hepatic encephalopathy may be seen in up to 50% of patients of chronic liver disease admitted to the hospital.[2] Development of hepatic encephalopathy seems unrelated to underlying etiology of liver cirrhosis. However increasing severity and frequency of HE episodes increase mortality risk[5]. HE is a potentially reversible, life threatening, severe neuro-psychiatric condition due to liver failure. It has been postulated that HE is caused by systemic accumulation of certain GIT-derived neurotoxins especially hyperammonemia in patients with hepatic dysfunction and increased porto-systemic blood shunting[11]. Therefore the treatment therapies in HE rely on reducing the neurotoxin and nitrogenous load from the gastro-intestinal track[11]. Rifaximin is an oral antimicrobial which is minimally absorbed from the gut and has a broad spectrum of action against anaerobes, gram-negative and gram-positive enteric bacteria with low risk of resistance[12]. The objective of present study was to find out the frequency of recurrence of hepatic encephalopathy in patients of chronic liver disease treated with rifixamin, so that appropriate adjustment to therapy may be made in such patients to reduce disease burden, morbidity and mortality.

The findings of our study are in agreement with the study by Bass et al.[8] who reported recurrence of HE in 22.1% of patients treated with rifaximin versus 45.9% in placebo group. Larsen et al.[9] reported rifaximin to be effective and safe in treatment of hepatic encephalopathy by improving cognitive, behavioral abnormalities and altered mental status linked to HE. In treatment of hepatic encephalopathy, Butt el al.[10] demonstrated improvement in 67.6% patients treated with Rifaximin as compared to 58.4% in patients without rifaximin. Brisk improvement in features of encephalopathy has been seen with rifaximin when compared to non-absorbable disaccharides (lactulose). Rifaximin also leads to shorter hospital stay duration and thereby reducing financial burden. Gastrointestinal disturbance is a common adverse effect of rifaximin but is usually mild and settles within a few days of treatment initation. There are numerous other complications of liver cirrhosis also. Khan et al.[13] reported hyponatremia in 40.1% of liver cirrhosis patients with hepatic encephalopathy and 8.1% patients expired. The Study by Ahmad et al.[14] demonstrates pulmonary hypertension to be present in 15% patients of Chronic liver disease while 3.6% had severe pulmonary hypertension. Habib et al.[15] reported depression and anxiety to be significantly higher in patients of chronic liver disease. Therefore adequate treatment of liver cirrhosis patients will also help in reduce morbidity and mortality.

The present study is different from other studies because it examines the prophylactic effect of rifaximin to prevent hepatic encephalopathy rather than effect as treatment of HE. Based on the results of this study, we conclude that the frequency of recurrence of hepatic encephalopathy due to chronic liver disease was significantly low in patients treated with rifixamin. We recommend adding Rifaximin to management therapy of patients to prevent further HE episodes so that disease burden, morbidity and mortality may be reduced. Our study has a few shortcomings also which should to be considered. A single center based study, the sample size was relatively small. Randomized Controlled Trials and cohort studies are better options but need more time and resources. Based on the findings of current study, further studies may be planned to gather further evidence.

CONCLUSION

We conclude that frequency of recurrence of hepatic encephalopathy is significantly lower in Rifaximin treated patients.
Recommendations: Rifaximin is a minimally absorbed, oral antibiotic with broad spectrum of action and has relatively few adverse effects. On the basis of results of this study on patients of chronic liver disease, frequency of recurrence of hepatic encephalopathy was significantly less in patients treated with rifixamin as compared to placebo. Therefore we recommend prescription of Rifaximin to patients of chronic liver disease to prevent recurrence of Hepatic Encephalopathy to reduce disease burden, morbidity and mortality, thereby improving quality of life of these patients.
Author's Contributions: This study was conceived and designed by KA, FA and AATKK. NIB, OH and FA did the initial literature research and designed the proforma for data collection. KA, FA and FA did the data collection, assembly and patient assessment. Data analysis and interpretation was performed by NIB and OH. NIB, FA and AATKK were involved in manuscript writing. KA, OH and FA did the final critical review and corrections. NIB is the corresponding author on behalf of all other authors.
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