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ORIGINAL ARTICLE

Effectiveness And Clinical Effects of Long-Term Rifaximin in Cirrhotic Patients with Hepatic Encephalopathy

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ABSTRACT

Background: Rifaximin has emerged as a new primary treatment for the treatment and management of hepatic encephalopathy in cirrhosis patients. This study aimed to evaluate the efficacy of long-term rifaximin therapy and its clinical effects on hepatic encephalopathy in patients with liver cirrhosis.

Material and Methods: A retrospective cohort study was conducted in the Medicine Department of Nishtar Hospital, Multan from April 2022 to October 2023. A total of 100 liver cirrhosis patients were selected for the study by consecutive sampling. The patients were divided into two groups; the cohort group including 50 patients who were administered rifaximin for 6 months at our hospital and the control group including 50 patients who were not administered rifaximin. The primary end-point of our analysis was to assess the effectiveness of long-term rifaximin therapy and the secondary end-points were the effect of shunts and E.coli infection. The clinical outcomes between both groups were evaluated by measuring liver stiffness by magnetic resonance elastography using age, Child-Pugh score, incidence of hepatocellular carcinoma, and MRE as covariables.

Results: The baseline serum ammonia was 105 (60-296) in rifaximin group which decreased to 83 (33-152) after 14 days and 83 (44-190) after 60 weeks (p=0.001). Overt HE recurred in 2 patients during pleural drainage and self-interruption of the drug. Albumin, platelet count, total bilirubin, and prothrombin time did not change significantly after treatment. Adverse effects of rifaximin were presented in one patient (2%) in the form of diarrhea only. A total of 23 patients (46%) had shunts larger than 8mm with pretreatment ammonia of 110 (92-295) and 83 (52-148) after 6 months (p=0.001). The patients with shunts smaller than 8 mm had pretreatment ammonia of 100 (60-182) and 65 (42-145) post-treatment (P=0.040). 39 patients (78%) patients had two or more shunts with pretreatment ammonia of 102 (70-295) and 81.2 (42-149) after treatment (p<0.001).

Conclusion: Rifaximin is an effective and safe treatment regimen for the long-term treatment of hepatic encephalopathy in patients with liver cirrhosis. It reduces the serum ammonia levels and prevents E.coli infections, increasing survival. Ineffective rifaximin treatment was associated with portosystemic shunt diameter ≥ 8.

Keywords: Ammonia, Cirrhosis, Hepatic encephalopathy, Rifaximin

INTRODUCTION

Liver cirrhosis is a frequent condition caused by permanent scarring and damage to the liver tissue leading to impaired liver function.[1] Since it is stage 3 of liver disease, it progresses to liver failure and increases the risk of mortality. Cirrhosis also presents as complications such as ascites, hepatic encephalopathy, variceal bleeding, and jaundice.

Hepatic encephalopathy is a common complication in cirrhotic patients occurring in 30-45% of patients.[2] HE is the gradual or sudden onset of neurological and psychological dysfunction that can range from changes and behavior (stage I) and lethargy (stage III) to a comatose state (stage IV).[3] Stage IV HE also known as overt HE indicates poor patient prognosis with a mortality rate of 65% in one year and 85% in a five-year analysis. Minimal HE can also affect prognosis and increase the risk of morbidity.

The primary treatment of hepatic encephalopathy is antibiotic treatment with lactulose or rifaximin[4]. However, literature in the U.S. and Europe have recommended rifaximin over lactulose since due to its long-term effects, it prevents the incidence and recurrence of overt hepatic encephalopathy and decreases the risk of morbidity.[5, 6]Studies have also reported an excellent efficacy of the combined use of lactulose and rifaximin in complete recovery, decreasingthe risk of morbidity and mortality.[7]

In Pakistan, the short-term use of rifaximin has shown positive results.[8] However, no study has yet been conducted to assess the long-term clinical use and impact of rifaximin and its association with spontaneous portosystemic shunts. We conducted this study to evaluate the efficacy of long-term rifaximin therapy and its clinical effects on hepatic encephalopathy in patients with liver cirrhosis.

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MATERIAL AND METHODS

A retrospective cohort study was conducted in the Medicine Department of Nishtar Hospital, Multan from April 2022 to October 2023. A total of 100 liver cirrhosis patients were selected for the study by consecutive sampling. The sample size was calculated by keeping 95% CI, 5% margin of error, and 50% population in Epi Info software. All patients provided their informed consent to become a part of the study. The ethical committee approved the study.

The patients were divided into two groups; the cohort group including 50 patients who were administered rifaximin for 6 months at our hospital and the control group including 50 patients who were not administered rifaximin. The primary end-point of our analysis was to assess the effectiveness of long-term rifaximin therapy and the secondary end-points were the effect of shunts and E.coli infection. The clinical outcomes between both groups were evaluated by measuring liver stiffness by magnetic resonance elastography using age, Child-Pugh score, incidence of hepatocellular carcinoma, and MRE as covariables. MRE was measured at the start of rifaximin therapy by using 3.0-T imagers.

We classified shunts larger than 8mm in the large group and shunts smaller than 8mm in the small group to evaluate the effect of the size of the shunt. Shunts were assessed during HCC follow-up by contrast-enhanced CT images. In case of more than one shunt, the diameter of the largest shunt was considered.

All data was analyzed by SPSS version 24. Categorical variables were compared by Fisher's exact test and were presented in percentages. Continuous variables were presented as median and were compared by the Mann-Whitney U test and paired variables were compared by the Wilcoxon rank test. Overall survival between both groups was measured by comparing measures of MRE. Propensity score matching was done by multiple logistic analysis to eliminate the effect of patient selection on outcome variables. Kaplan-Meier method was used to measure mortality and the log-rank test was used to compare mortality

between both groups. A two-tailed p-value less than 0.05 was taken significantly.

RESULTS

A total of 100 patients with liver disease were included for analysis among which 50 were administered rifaximin for 6 months. In cohorts, 30% had a history of overt HE, 24% had hepatocellular carcinoma and 70% had esophageal varices. In 76% of patients, lactulose was administered in combination with lactulose, and in 64% of patients BCAA was administered in combination with rifaximin. The baseline characteristics of patients of both groups are shown in Table I.

The baseline Serum ammonia was 105 (60-296) in the rifaximin group which decreased to 83 (33-152) after 14 days and 83 (44-190) after 60 weeks (p=0.001). Overt HE recurred in 2 patients during pleural drainage and self-interruption of the drug. Albumin, platelet count, total bilirubin, and prothrombin time did not change significantly after treatment. Adverse effects of rifaximin were presented in one patient (2%) in the form of diarrhea only.

Table 1: Patients' Baseline Parameters

	Cohort group (n=50)	**Control group (n=50)**	**P value**
Median age	70 (39-85)	70.5 (41-89)	0.929
Gender			0.240
Male	23 (46%)	15 (30%)	
Female	27 (54%)	35 (70%)	
Median BMI	25.82 (19.70-34.91)	24.3 (16.6-29.8)	0.039
Etiology of liver cirrhosis			0.110
Viral hepatitis B	20 (40%)	10 (20%)	
Viral hepatitis C	16 (32%)	25 (50%)	
Non-alcoholic fatty liver disease	4 (8%)	15 (30%)	
Child-Pugh classification			0.048
A	20 (40%)	27 (54%)	
B	20 (40%)	21 (42%)	
C	10 (20%)	2 (4%)	
Albumin-Bilirubin grade			< 0.001
1	2 (4%)	29 (58%)	
2	35 (70%)	20 (40%)	
3	13 (26%)	1 (2%)	
MELD score	7 (3-18)	10 (0-23)	0.211
ALT	25.3 (9-106)	32.4 (9-1489)	0.112
AST	40.1 (21-135)	44 (16-1039)	0.432
Gamma-glutamyl transpeptidase	36.6 (12-560)	65 (15-505)	0.063
Serum ammonia	105 (60-296)	53 (24-90)	<0.001
Albumin	3 (2.5-4.6)	4.01 (2.7-5.0)	<0.001
Total bilirubin	1.70 (0.6-5.0)	1 (0.6-8.8)	0.001
Platelet count	9.0 (5.1-28.3)	12.6 (2.7-31.4)	0.025
Prothrombin activity	61 (39-135)	70 (15-110)	0.070
AFP	5.6 (1-3380)	7.19 (1.5-390.2)	0.069
DCP	38 (16-2180)	26 (10-11690)	0.378
Fibrosis 4 index	6.58 (1.67-14.9)	5.11 (1.5-34.7)	0.120
MRE	6.05 (4-10.10)	5.92 (4.45-11.8)	0.750
SWE	24.3 (9.1-55)	17.1 (8-35.6)	<0.001
History of overt hepatic encephalopathy	15 (30%)	-	<0.001
Hepatocellular carcinoma	12 (24%)	15 (30%)	0.439
Ascites	15 (30%)	13 (26%)	0.828
Esophageal varices	35 (70%)	30 (60%)	0.474
Max diameter of portosystemic shunts	7.8 (2.0-17.4)	5.1 (1.9-11.1)	<0.001
Number of shunts			0.001
0,1	11 (22%)	32 (64%)	
2 or more	39 (78%)	18 (36%)	
Administration of lactulose	38 (76%)	8 (16%)	<0.001
Branched-chain amino acid	32 (64%)	18 (36%)	0.040
Sarcopenia	23 (46%)	23 (46%)	1
Follow-up	62 (23-90)	90 (6-119)	<0.001

Table 2: Risk factors of insufficient improvement in serum ammonia after treatment

	Hazards ratio (95% CI)	P value
Univariable analysis		
≥ 70 years old	1.9 (0.61-8.9)	0.28
Male gender	0.489 (0.130-1.91)	0.32
BMI ≥ 28	0.38 (0.090-1.88)	0.27
AST ≥ 36	0.367 (0.090-1.53)	0.15
ALT ≥ 30	0.36 (0.08-1.9)	0.20
GGTP ≥ 42	0.66 (0.22-2.94)	0.62
Albumin < 3.0	3.6 (0.77-14)	0.089
Total bilirubin ≥ 1.4	4 (0.78-13)	0.09
Platelet count < 6.8	3.9 (0.73-24)	0.10
Prothrombin ≥ 58	2.7 (0.68-12)	0.10
AFP ≥ 6.5	3.11 (0.61-18)	0.18
DCP ≥ 18	3.8 (0.62-22)	0.14
Presence of ascites	2.3 (0.68-9.0)	0.15
Presence of esophageal varices	2.0 (0.46-7.8)	0.39
History of HE	3.8 (0.81-15)	0.08
Presence of HCC	0.77 (0.20-3.5)	0.67
Presence of sarcopenia	1.60 (0.35-6.4)	0.51
Child-Pugh score ≥ 7	4.1 (0.96-15)	0.058
ALBI ≥ -1.6	5.5 (1-24)	0.029
MELD ≥ 12	2.8 (0.69-12)	0.09
Fibrosis 4 index ≥ 8.3	0.38 (0.097-2.1)	0.28
MRE ≥ 5.0	1.60 (0.36-8.5)	0.40
SWE ≥ 17.7	2.7 (0.68-13)	0.18
Diameter of shunt ≥ 8	7.2 (1.6-32)	0.020
2 or more shunts	1.40 (0.35-6.0)	0.71
Multi-variable analysis		
Diameter of shunt ≥ 8	5.8 (1.0-27)	0.040
ALBI ≥ -1.6	3.0 (0.56-17)	0.18

A total of 23 patients (46%) had shunts larger than 8mm with pretreatment ammonia of 110 (92-295) and 83 (52-148) after 6 months (p=0.001). The patients with stunts smaller than 8 mm had pretreatment ammonia of 100 (60-182) and 65 (42-145) post-treatment (P=0.040). 39 patients (78%) patients had two or more shunts with pretreatment ammonia of 102 (70-295) and 81.2 (42-149) after treatment (p<0.001).

A less improvement in ammonia levels after treatment was related to shunt diameter and ALBI score. However multivariable analysis showed that insufficient improvement in ammonia was independently related to shunt length equal to or longer than 8 mm (Table II).

The mean follow-up was 62 weeks in cohorts and 90 weeks in controls. Six patients (12%) died in the cohort group by liver failure or pleurodesis. Patients with Child-Pugh C had the shortest survival span. Seven patients (14%) died in the control group due to hepatic insufficiency, cardiovascular disease, or disseminated intravascular coagulation The difference in survival rate between both groups was insignificant (p=0.890).

DISCUSSION

Hepatic encephalopathy is a common complication occurring in up to 45% of cirrhotic patients. Rifaximin has emerged as a new primary treatment for the treatment and management of HE. We conducted this study to test the 6-month efficacy and clinical effects of rifaximin in cirrhosis patients and its association with shunts and E-coli infection. The results revealed that a decline in ammonia levels occurred 14 days after treatment and remained significantly lower up to 6 months. HE recurrence was only reported in 2 patients (4%) and diarrhea as an adverse effect was seen in 1 patient only. These results suggest that rifaximin is an effective and safe regimen for long-term treatment of HE. The efficacy and safety of rifaximin are also reported by previous studies conducted in Europe and the Americas.[9, 10, 11]

The HE recurrence in our study occurred due to pleural drainage which may be due to dehydration, infections, or intestinal hemorrhage. HE is assessed by West Haven criteria and the Trail Making test, however, the latter was not performed in our study. The shunts larger than 8mm were 50% in the cohort group and

12% in controls which indicated a strong correlation between hepatic encephalopathy and the development of shunts. Other studies also concluded that portosystemic shunts were significantly associated with ammonia levels.[12, 13] This finding was also reported in the present study.

No studies have been previously conducted to evaluate the relationship between shunts and rifaximin treatment. However, the findings of our study showed that rifaximin can help reduce ammonia levels for up to 6 months and improve encephalopathy, especially in patients who developed large shunts (≥ 8 mm). Ammonia levels did not decline in some patients which was independently related to large shunt diameter. This finding suggests that overt HE is improved by rifaximin therapy but this treatment may not be effective for minimal HE patients with large shunts and the shunt diameter was associated with ammonia levels. Previous literature also backs this finding.[14, 15, 16]Surgery or interventional radiology is recommended for whom rifaximin is not effective.

It has been reported previously that cirrhosis alters the function of gut microbiome which increases the risk of mortality.[17] In our study, one patient died due to an intestinal bacterial infection although none patients had SBP. This indicates that rifaximin prevents E.coli infections. Both groups also did not differ significantly with respect to survival rates but the shortest survival was observed in cohort patients with Child C, suggesting that rifaximin has limited efficacy in treating cirrhosis itself.

Our study has some limitations. We did not diagnose minimal HE so the effectiveness of rifaximin for it could not be found. Secondly, there was no protocol for starting treatment other than the instinct of the physicians. Thirdly, we did not assess the incidence of HCC, cardiovascular disease, infection, and malnutrition as causes of mortality in patients.

CONCLUSION

Rifaximin is an effective and safe treatment regimen for the long-term treatment of hepatic encephalopathy in patients with liver cirrhosis. It reduces the serum ammonia levels and prevents E.coli infections, increasing survival. Ineffective rifaximin treatment was associated with portosystemic shunt diameter ≥ 8.

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