RIFAXIMIN EFFECTIVENESS IN PREVENTING THE RECURRENCE OF HEPATIC ENCEPHALOPATHY AMONG PATIENTS WITH LIVER CIRRHOSIS

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ABSTRACT

Objective: To determine the effectiveness of rifaximin in reducing the frequency of recurrence of hepatic encephalopathy among patients with liver cirrhosis.

Study Design: Descriptive case series.

Place and Duration of Study: Outpatient department of Combined Military Hospital Peshawar from Jan to Jun 2017.

Methodology: We included one hundred patients of either gender having liver cirrhosis with child Pugh B or C class with at least two previous episodes of hepatic encephalopathy. Patients were followed for six months to have any recurrence of hepatic encephalopathy. Conventional group was defined as having standard regimen including lactulose. Rifaximin treatment was defined as a 550mg BD daily dosing along with standard prescription.

Results: Fifty patients were on conventional treatment to prevent recurrence of hepatic encephalopathy while 50 patients were using rifaximin in addition to standard prescription. The average age of 54.8 ± 6.1 years with 58% male patients and 48% in child-pugh B class. Thirty (30%) patients developed hepatic encephalopathy among the study population. 14 patients with recurrence belong to rifaximin group while 16 were on conventional treatment (p-value >0.05) showing a non-significant difference. Post stratification revealed only age as a significant predictor of recurrence of hepatic encephalopathy in our study population (p<0.05).

Conclusion: Frequency of hepatic encephalopathy is similar in conventional treatment with Lactulose over six months of follow up as compared with rifaximin.

Keywords: Decompensated liver disease, Hepatic encephalopathy, Lactulose, Rifaximin.

INTRODUCTION

About 150 million people are chronically infected with hepatitis C virus, and >350000 people die every year1-3. Countries with high rates of chronic infection are Egypt (22%), Pakistan (4.8%) and China (3.2%)4. Hepatic encephalopathy (HE) represents a continuum of transient and reversible neurologic and psychiatric dysfunction5-7. As more data emerge, it is hoped that HE will become a more easily complicated complication of decompensated liver disease. Five Hepatic encephalopathy occurs in approximately 30-45% of patients with cirrhosis and 10-50% of patients with trans jugular intrahepatic portosystemic shunt, while minimal hepatic encephalopathy affects approximately 20-60% of patients with liver disease6,8. Treatment strategies are directed at increased elimination or reduction of gut-derived ammonia in addition to correction of dynamic conditions that provoke bouts of HE9-10. The standard of care for treatment of acute HE is lactulose, a non absorbable disaccharide that is thought to increase elimination and reduce absorption of ammonia. Although lactulose seems to work in the acute setting, but for durability of remission different antibiotics have to be used7.

In a study done to determine long term remission of HE by Rifaximin over 6 months, breakthrough episode of hepatic encephalopathy occurred in 22.1% of patients in the rifaximin group, as compared with 45.9% of patients in the placebo group. A total of 13.6% of the patients in the rifaximin group had a hospitalization involving hepatic encephalopathy, as compared with 22.6% of patients in the placebo group (p=0.01)7. In another RCT investigating the efficacy of rifaximin over a 6-month period in reducing the risk of recurrent HE in patients at baseline, but with a history of at least two bouts of acute HE in the previous 6 months prior to enrollment, a total of 299 patients were randomized to receive rifaximin or placebo. Compared with placebo, patients at high risk for recurrent HE in the rifaximin group had highly statistically significant reductions in bouts of acute HE (58%) and reductions in hospitalizations related to HE (50%) over a 6-month period8.

Pakistani population is unique in dietary habits and gut flora due to different consumption of meat when compared to western population. There are few studies available in Pakistan showing the role of

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rifaximin in reducing the risk of recurrent encephalo-
pathy. The current study will help reduce episodes 
of HE in Pakistani cirrhotic patients. This study will 
enable us to reduce mortality in Chronic Liver Disease 
patients secondary to Hepatic Encephalopathy and 
decrease burden of indoor patients in our overloaded 
hospitals.

**METHODOLOGY**

This descriptive case series study was conducted 
in Outpatient department of Combined Military Hos-
pital Peshawar, form January to June 2017. Sample size 
using 95% confidence interval, 5% level of significance 
and 80% power of study, an incident of hepatic encepha-
lopathy observed in 22% of patients in the rifaximin 
group in comparison to 46% of patients in the placebo 
group, sample size was 100. Consecutive non probabi-
listy was sampling technique. Criteria was including 
both male and female sex, age 45-65 years, diagnosed 
case of CLD with cirrhosis (USG Abdomen findings), 
history of at least 2 episodes of previous HE, grade 
B or C Child Pugh Classification of CLD. (Child pugh 
classification included severity of encephalopathy, 
Bilirubin Level, Albumin Level, Prothrombin time, and 
Ascites, Child B had score of 7-9, Child C >9). Exclusion 
criteria included renal Failure patients determined 
by hemodialysis or estimated GFR, diabetics as deter-
mined by history, anemia (Hb<8 g/dl), electrolyte ab-
normality (serum Na <125 mmol/l, K<2.5 mmol/l), 
waiting for Liver transplant.

The study was carried out after taking approval 
from ethical committee of Combined Military Hospital 
Peshawar, and all included patients were briefed and 
informed consent was taken from them from their 
permission. All bewildering variables were acknow-
ledged and excluded through inclusion and ruling out 
criteria. Patients from OPD of Combined Military Hos-
pital Peshawar were followed for 6 months. Rifaximin 
treatment was defined as a 550mg BD daily dosing 
along with standard prescription. Conventional group 
was defined as having standard regimen including lac-
tulose. Time since diagnosis and severity of CLD by 
Child Pugh classification was taken as effect modifier. 
Enrolled patients were followed for 6 months for onset 
of hepatic encephalopathy. Follow ups were ensured 
by contact no. Treatment was halted on first episode of 
hepatic encephalopathy and subsequently recorded.

Data analysis was performed using SPSS-16. Des-
criptive statics were used to measure qualitative and 
quantitative variables. Qualitative like gender, grade B, 
C Child pugh classification were measured as freq-
encies and percentages. Quantitative like age, episo-
des of previous HE was measured by mean standard 
development. Recurrence between two groups was com-
pared by chi-square test to be applied. Post stratifica-
tion chi-square test was applied. The p-value of ≤0.05 
was considered statistically significant.

**RESULTS**

Fifty patients were on conventional treatment to 
prevent recurrence of hepatic encephalopathy while 
50 patients were using rifaximin in addition to stan-
dard prescription. The average age of 54.8 ± 6.1 years 
with 58% male patients and 48% in child-pugh B class. 
Thirty (30%) patients developed hepatic encephalo-
pathy among the study population (table-I).

<p>| Table-I: Socio-demographic profile of study sample (n=100). |</p>
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>45-55 years</td>
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<td>≥56 years</td>
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<tr>
<td>Gender</td>
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</tr>
<tr>
<td></td>
<td>Female</td>
</tr>
<tr>
<td>Classification</td>
<td>Child Pugh Class B</td>
</tr>
<tr>
<td></td>
<td>Child Pugh Class C</td>
</tr>
<tr>
<td>Treatment</td>
<td>Conventional</td>
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<td>Rifaximin</td>
</tr>
<tr>
<td>Recurrence of hepatic Encephalopathy</td>
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</table>

Fourteen patients with recurrence belong to rifa-
imin group while 16 were on conventional treatment 
(p-value >0.05) showing a non-significant difference 
table-II).

Post stratification revealed only age as a signifi-
cant predictor of recurrence of hepatic encephalopathy 
in our study population (p<0.05) (table-III).

**DISCUSSION**

The development of hepatic encephalopathy will 
have clinical outcome that depends on child Pugh 
class11. Some patients with worse clinical picture may 
 improve while others with intermediate/mild clinical 
picture may deteriorate. In case of acute liver failure, 
 patients with hepatic encephalopathy may deteriorate 
from neurological complications such as cerebral ede-
ma, seizures, and intracranial hemorrhage7-10. As in 
cirrhosis, clinical outcome can be determined by child 
pugh class including five parameters (Grade of ence-
phalopathy, Ascites, Albumin Level, Bilirubin level, 
Prothrombin time/International normalization ratio)11. 
Hepatic encephalopathy is a clinical outcome of liver
Hepatic Encephalopathy


cirrhosis and its symptoms range from slight lack of awareness and mild impairment of coagulated function to deep coma. The gamut of HE encompasses all causes related to functionality of liver patients is hyperactive senseless so it makes a heavy burden both on patient’s family and attending physician usually every 4th patient presenting to medical emergency belongs to decompensated chronic liver disease with various types of complications.

The management of hepatic encephalopathy includes use of lactulose in high dose, and it is a disaccharide that is not absorbed in the gut, rather it reduces the absorption of ammonia from gut, even great role in eliminating it as a part of its pharmacological action. Lactulose is very good in acute presentation of hepatic encephalopathy; however, recurrence rate is high if treatment is continued with lactulose. Many drugs/treatments have been tried to prevent recurrence of hepatic encephalopathy but none prove to be beneficial. Rifaximin is a semisynthetic poorly absorbed broad-spectrum antibiotic having low bioavailability that is considered to reduce ammonia production by eliminating ammonia producing gut bacteria.

In a comparative study done in Sheikh Zayed Hospital Lahore, Rifaximin failed to reduce the recurrence of hepatic encephalopathy when patients were followed for six months of duration. Lawrence et al described effects of Rifaximin on hepatic encephalopathy including neuropsychiatric syndrome, overt episodes, disorientation, psychomotor dysfunction, and other complications of cirrhosis and found it beneficial for treatment of recurrent hepatic encephalopathy. Levey et al, described improvement in grades of hepatic encephalopathy when being treated with rifaximin and also reduced hospital admission due to encephalopathy.

CONCLUSION

It is hereby deducted that frequency of recurrence of hepatic encephalopathy is similar in conventional treatment over 6 months of follow up in comparison to rifaximin. Remission beyond six months needs further evaluation.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

REFERENCES


Table-II: Association between treatment modality and baseline characteristics (n=100).

<table>
<thead>
<tr>
<th>Parameters</th>
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<td>14</td>
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Table-III: Association of age with the recurrence among patients with and without Rifaximin treatment.

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<td>Rifaximin</td>
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<tr>
<td>Age groups (≥56 years)</td>
<td>Conventional</td>
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<td>33</td>
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<td></td>
<td>Rifaximin</td>
<td>-</td>
<td>-</td>
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