Original Article

Role of Rifaximin in Prevention of Recurrent Hepatic Encephalopathy in Chronic Liver Disease

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ABSTRACT

Objectives: To determine the efficacy (in terms of recurrence) of rifaximin in Hepatic Encephalopathy (HE) in chronic liver disease.

Study design and setting: A descriptive study carried out from 4th September 2018 to 3rd March 2019 at the department of Medicine, Combined Military Hospital, Quetta.

Methodology: A total of 104 patients of chronic liver disease with HE, 25-65 years and both genders were included. Patients with gastrointestinal hemorrhage, chronic renal insufficiency and anemia were excluded. Then tab Rifaximin 550 mg twice daily along with standard prescription i.e. Lactulose 30 to 60 ml in two to three divided doses per day was given to each patient and efficacy was noted**.** Statistical analysis was carried out using SPSS version 20.0. Age, duration of disease and Conn's score was presented as mean and standard deviation. A p value = 0.05 was considered as significant

Results: Age range in our study was from 25 to 65 years with a mean of 45.73 ± 8.13 years. Most of the patients 54 (51.92%) were between 46 to 65 years of age range. Out of the 104 patients, 77 (74.04%) were male and male to female ratio was 2.9:1. Mean duration of disease was 13.66 ± 3.77 months. Mean conn's score was 4.77 ± 1.43. Efficacy (no recurrence) of rifaximin in HE in chronic liver disease was found in 85 (81.73%) patients.

Conclusion: It was inferred that rifaximin is useful in decreasing the recurrence of HE in chronic liver disease patients with previous episode/s of encephalopathy.

Keywords: End stage liver disease, Hepatic encephalopathy, Rifaximin

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INTRODUCTION:

Hepatic Encephalopathy (HE) is one of the most challenging complications of advanced liver disease. It can be defined as "a neuropsychiatric syndrome caused by porto-systemic venous shunting, ranging from minimal to overt HE or coma". HE occurs in as many as about 30%–45% of patients with cirrhosis while corresponding figure for patients who have undergone TIPS (transjugular intrahepatic porto-systemic shunt) is 10-50%. Minimal HE which is only detected with psychometric analysis is seen in approximately 20%–60% of patients with cirrhosis.[1]

Therapies for HE mainly aim at reducing the nitrogen load in the gut, as it is hypothesized that increased concentration of ammonia is the major abnormality, in patients with abnormal liver functional tests (LFTs) and porto-systemic shunting.[2] Lactulose, a non-absorbable synthetic disaccharide, by bacterial action results in acidification of colonic contents which facilitates the formation of non-absorbable NH_4 ion from NH_3. It also alters bowel flora so that fewer ammonia-forming organisms are present.[3] Non-absorbable disaccharides have been proved to be effective both in management and prevention of HE with a mortality benefit as compared to placebo.[4] Although lactulose seems to work in the acute setting, for durability of remission, different antibiotics have to be used. Several agents have been used for this purpose but rifaximin is by far the most

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frequently used antibiotic treatment for this indication i.e. prevention of recurrent HE.

As mentioned earlier; lactulose and rifaximin are the most commonly used agents for prevention of recurrent HE. However, compliance to lactulose is often limited due to adverse effects.[5] For this same reason, rifaximin is rapidly evolving as a therapy of first choice to decrease the incidence of recurrent HE. Rifaximin, a rifamycin derivative, is an oral antibiotic having a broad spectrum of activity and low risk of bacterial resistance which is absorbed through the intestinal mucosa in negligible amounts.[6] In different studies rate of recurrence of HE with Riafaximin treatment has been reported from 22.1% to 36.5%.[7] A Spanish study by Morillas et al[8] also showed that Rifaximin was effective in preventing and improving quality of life in patients with cironic liver disease. A recent meta analysis by Hudson and Schuchmann showed that adding rifaximin to lactulose was more effective in long term treatment of HE than lactulose alone[9]. Multiple treatment agents/strategies have been studied for treatment of HE , some (e.g. branched chain amino acids[10], L-ornithine L -aspartate[11], nutritional therapy[12]) were found to have some benefit while others (e.g. Acetyl L –Carnitine[13], Flumezanil[14], probiotics)[15] did not show any significant benefit, or the studies were inconclusive. These agents, therefore, have lost interest of clinicians, and are not being used routinely in clinical practice.

Above mentioned studies are from western researchers and have wide variations in results. This study was carried out to find out if Rifaximin has the same efficacy in preventing recurrence of HE in Pakistani population because it is an established fact that there is a difference of dietary habits and living styles as well as genetic makeup between Pakistani and western populations. While there are several studies[16,17] assessing role of rifaximin in treating HE, there are only a few[7] which have assessed its role in preventing HE recurrence. More data in this regard will provide better evidence to choose this medicine for this purpose or otherwise in Pakistani population.

METHODOLOGY:

It was a descriptive study for which Institutional review board of CMH Quetta issued a certificate for the study vide number CMH QTA-IRB 018.

All patients of chronic liver disease with history of at least one episode of HE (as per-operational definition). Duration of disease was >6 months. Child Pugh Class of A, B & C (these were not the source of bias as they were stratified in the final analysis). Patients 25-65 years of age and both gender were included in the study.

Exclusion criteria were patients with known hypersensitivity to rifamixin or excipients used in its formulation. Patients with psychiatric disorders (since diagnosing HE may be difficult due to comorbidity) which remain uncontrolled

For this study we defined hepatic encephalopathy as "new onset of overt neuropsychiatric abnormality/ies in a patient with pre-existing chronic liver disease'. Patients were labeled as having HE only when there was no competing pathology present to explain neuropsychiatric abnormality. Minimal (covert) hepatic encephalopathy, therefore, was not actively looked for and was not included in the study.

Total number of 104 patients of chronic liver disease with HE (as per operational definition) meeting the inclusion criteria were enrolled. Sample size of 104 cases had been calculated with 95% confidence level, 8% margin of error and assuming a recurrence rate of rifaximin in hepatic encephalopathy in chronic liver disease at 22.1%. Patients were given details of the study and an informed consent was obtained for enrollment. After taking informed written consent, Child-Pugh class was calculated. Tab Rifaximin 550 mg twice daily along with standard prescription i.e. Lactulose 30 to 60 ml in two to three divided doses per day was given to each patient and recurrence of hepatic encephalopathy was noted over a mean duration of 13.66 ± 3.77 months. All data was recorded on a specially designed proforma.

Statistical analysis was carried out using SPSS version 20.0. Age, duration of disease and Conn's score was presented as mean and standard deviation. Gender, child pugh class (A/B/C) and efficacy (yes/no) was presented as frequency and percentage.

Different possible confounding variables like age, gender, duration of disease and Child Pugh Class (A/B/C) were controlled by stratifying patients according to the values obtained. Post-stratification chi square was used to calculate their impact on efficacy. P value < 0.05 was considered as statisticially significant.

RESULTS:

Age range of patients in our study was from 25 to 65 years with a mean of 45.73 ± 8.13 years. Most of the patients 54 (51.92%) were between 46 to 65 years of age.

Out of the 104 patients, 77 (74.04%) were male with male to female ratio being 2.9:1 (Figure II). Mean duration of disease was 13.66 ± 3.77 months. Mean Conn's score was 4.77 ± 1.43. There were no drop outs or deaths during the period of this study. Distribution of patients with other confounding variables is shown in Table I.

Rifaximin was found to be effective (no recurrence) in HE in chronic liver disease was found in 85 (81.73%) patients. There was no significant difference between different age groups and genders (Table II). Table II also shows efficacy of Rifaximin with respect to duration of

disease and Child Pugh Class respectively.

DISCUSSION:

In this study the overall recurrence rate on Rifaximin was 18.2%. This is in keeping with the corresponding rate in study which reported a recurrence rate of 22.1% with rifaximin.[18] In another study by Ali et al, rate of recurrence of HE was 36.51%.[7] This minor difference may possibly be due to a smaller number of patients in study by Ali et al which enrolled only 63 patients in treatment group. However this can be further evaluated by enrolling a larger number of patients in future studies.

After oral administration, intestinal absorption of Rifaximin is negligible and the drug is concentrated in the lumen of the intestine. It has a reasonably wide-spectrum and has been shown to have in vitro activity against gram-positive as well as gram-negative aerobic and anaerobic intestinal bacteria. It has very low risk of generating bacterial resistance.[18] Randomized controlled studies have shown that rifaximin was more effective than non-absorbable disaccharides and was as effective as or more effective than other antibiotic drugs used in the treatment of acute HE.[19]

The study of Sanyal et al[20] concluded that patients taking a combination of lactulose and rifaximin had higher scores on health related quality of life questionnaires (HRQL). This is in keeping with efficacy of this combination for prevention of recurrent HE as in the same study the authors found that a deterioration in HRQL scores was associated with episodes of HE. We can therefore infer that by reducing the recurrence of HE, rifaximin improves quality of life of CLD patients.

Table I: Stratification of patients with different confounding variables (n=104)

Confounding variables		Frequency %age
Duration of CLD (months)	=12	32 (30.77)
	>12	72 (69.23)
Child Pugh Class	A	28 (26.92)
	B	57 (54.81)
	C	19 (18.27)

Table II: Efficacy of Rifaximin according to different variables

		Efficacy		P-value*
		Yes	No	
Age (years)	25-45	41	09	0.945
	46-65	44	10	
Gender	Male	65	12	0.231
	Female	20	07	
Duration of CLD (Months)	=12	29	03	0.118
	>12	56	16	
Child Pugh Class	A	23	05	0.588
	B	48	09	
	C	14	05	

*chi-Square

Rifaximin was used in addition to lactulose in this study patients, which is the most commonly combination used to treat acute HE and is also recommended in patients who have recurrence of HE on non absorbable disaccharides alone. The debate whether to use rifaximin either instead of or in addition to lactulose has persisted in spite of current practice guidelines which recommend lactulose as first-line treatment. In study by Morillas RM[8,] Rifaximin was effective when compared to placebo in 299 patients with history of recurrent encephalopathy (HE) in remission. Rifaximin 550 mg twice daily decreased the risk of recurrent episode of HE as well as the risk of hospitalization from HE. It is worth noting that more than 90% of patients in each arm of this study were taking lactulose at baseline. When further studied, it was revealed that patients who did not use lactulose at baseline did not have significantly different outcomes with rifaximin compared to placebo. Overall, treatment with rifaximin was well tolerated with positive outcomes[21]. We therefore did not include a Rifaximin only arm in our study.

Each successive episode of overt HE may leave increasing residual deficits in working memory, response inhibition as well as learning when patients are assessed by psychometric testing[22]. Standard treatment for an acute episode of HE includes non-absorbable antibiotics (such as rifaximin), lactulose or lactitol and correction of any precipitating factor. Patients with minimal (covert) HE need psychometric analysis for diagnosis which were not included in our study. We did not carry out detailed cognitive evaluation to diagnose minimal HE and this remains a topic for research. As mentioned earlier successive episodes of HE inflict progressive incremental loss of cognitive functions but in order to be diagnosed with confidence, such a loss will need repeated psychometric testing. It can thus be questioned if patients taking rifaximin any difference as regards cognitive function when compared to those who do not receive such treatment. Further research can address this very question looking at the loss of cognitive functions in patients with liver cirrhosis and making comparison between patients taking rifaximin and those who do not take any treatment.

Limitations of this study include a relatively smaller number of patients, and the fact that we did not stratify the response of treatment according to various precipitating factors for hepatic encephalopathy. It might be possible that rifaximin is more effective for one or more particular triggers of hepatic encephalopathy than others. Therefore it is recommended that any future researchers enroll larger number of participants and

stratify their results according to the different triggers identified. Future researchers may also look into cognitive functions of patients on and off treatment over a period of time.

CONCLUSION:

Results of this study showed that rifaximin is an effective agent for reducing the recurrence of HE in chronic liver disease patients. However, due to small size of our study, further research enrolling larger number of patients with randomization will provide further evidence for or against this statement.

Authors Contribution:
Sahar Farzand: Conception, Design, Data Collection & Analysis
Abdul Latif Khattak: Conception & Design
Rafi ud Din: Data Collection & Analysis, Drafting
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Shahzeb Ahmed Satti: Data Collection & Analysis

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