

# A Comparison of Rifaximin with Placebo for the treatment of Hepatic Encephalopathy

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## ABSTRACT

**Background:** The treatment options for HE is majorly based or focuses the cure of episodes as they occur and also directed to reduce the nitrogenous load in the gut. The underlying drug rifaximin is simply oral absorbable antimicrobial mediator, which is condensed in the gastrointestinal tract. It has broad-spectrum activity i.e. in vitro activity against all gram positive and gram-negative bacteria including aerobic and anaerobic.

**Methods:** The study design opted for the present research was interventional, where the hepatic encephalopathy patients were given randomly rifaximin and placebo treatment. The study duration was of six month from january to june 2017. The venue of the study was Lahore general hospital. The exclusion criteria include all patients with liver transplantation, precipitants of hepatic encephalopathy, respiratory problems and anemia whereas all the patients of both genders above 18 years of age with minimum of two evident encephalopathy episodes were included in this study.

**Results:** A total of 120 patients were recruited for this study. The mean age of the patients was  $44 \pm 8.9$  with range 18-55. The average treatment duration observed in rifaximin group was  $128.1 \pm 45$  whereas in placebo group was  $110 \pm 61.2$  days. We also observed high compliance rate between both groups i.e. 83.2% & 84.1%. We observed the breakthrough episode of HE in 15 (25%) of the patients in rifaximin group where as it is 30(50%) in placebo group. The hazard ratio was 0.39 for the breakthrough episode risk in rifaximin group in comparison to placebo group.

**Conclusion:** We may conclude a robust protective effect of rifaximin alongside episodes of hepatic HE. It also diminishes the risk of hospitalization.

**Keywords:** Rifaximin, hospitalization, Quality of Life (QoL), hepatic encephalopathy (HE)

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## INTRODUCTION

Almost 5.5 million people in United States (US) experiencing hepatic cirrhosis (HC) disease and this disease is one of the major causes of deaths<sup>1,2,3</sup>. The complication of HC named hepatic encephalopathy (HE) forces arduous burden to the patients, his family and the entire health system<sup>1,4</sup>. Explicit outbreaks of HE are devastating and can occur deprived of admonition, reduce the patient capability of self-care and hospitalization<sup>1,4</sup>. An estimated 40000 patients were hospitalized In 2003 with HE disease, also an increase of number was observed in 2004 to 50000<sup>4</sup>. Though the manifestation of outbreaks of HE appears to be dissimilar to the source of cirrhosis<sup>5</sup>, increases in the incidence and ruthlessness of such outbreaks forecast an increased risk of death<sup>6</sup>. The treatment options for HE is majorly based or focuses the cure of episodes as they occur and also directed to reduce the nitrogenous load in the gut<sup>7</sup>. The existing standard of care for patients with HE, management with non-absorbable disaccharides lactitol or

lactulose, decreases the fascination of ammonia through liberating upshots and by shifting the colonic pH<sup>8,9</sup>. The underlying drug rifaximin is simply oral absorbable antimicrobial mediator, which is condensed in the gastrointestinal tract. It has broad-spectrum activity i.e. in vitro activity against all gram positive and gram-negative bacteria including aerobic and anaerobic. Also this drug has low risk of persuading bacterial resistance<sup>10,11,12</sup>. The main of the study was to determine the efficacy and safety of the rifaximin drug in comparison to a placebo treatment in patients with HE.

## MATERIAL AND METHODS

The study design opted for the present research was interventional, where the hepatic encephalopathy patients were given randomly rifaximin and placebo treatment. The study duration was of six month from january to june 2017 . The venue of the study was Lahore general hospital. The exclusion criteria include all patients with liver transplantation, precipitants of hepatic encephalopathy, respiratory problems and anemia whereas all the patients of both genders above 18 years of age with minimum of two evident encephalopathy episodes were included in

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this study. The patients were screened at first and observed for a certain period of time and then enrolled for the study. The treatment allocation was applied randomly a bunch of patients were provided with rifaximin and others with Placebo. Demographics information along with diagnostic history of all the participants was collected via a standard face-to-face interview. Other socioeconomic status, dietary habits, life style etc. was also noted. All the required diagnostic values were assessed from the blood samples and radiographic taken in hospital laboratory. An informed consent was also taken from the patients. Ethical consideration was taken in to account by taking approval Hospital ethical Committee.

**Statistical analysis:** All the collected data was stored electronically & analyzed later by using SPSS version 20. Descriptive statistics were applied to calculate mean and standard deviation. Frequency distribution and percentages were calculated for qualitative variables like gender, Conn score etc. Over all a P values less than 0.05 was considered statistically significant.

## RESULTS

A total of 120 patients were recruited for this study. The mean age of the patients was  $44 \pm 8.9$  with range 18-55. 80(66.6%) of the patient were in the age category of 36 to 45. Whereas 30(25%) belong to 18-35 and 10(8.4%) were above and equal 45 years of age. 78(65%) of the patients were male and 42(35%) were females. The two treatments rifaximin and placebo were provided into equal number of patients i.e., 1:1 thus dividing the sample into two groups. As per the study protocol, we discontinued the treatment drug at first breakthrough episode of HE. The numbers of early drug withdrawal, due to all other reasons in both groups. The demographic characteristics are given in table 1.

Table 1: The baseline characteristics of HE patients.

Characteristic	Rifaximin	Placebo
Age	43+8.6	45+9.2
<b>Age groups</b>		
18-35	14(23.3%)	16(26.66%)
36-45	38(63.3%)	42(70%)
Above 45	7(11.6%)	3(5%)
Duration of current remission (days)	65.7+42.3	71.2+49.3
<b>Number of HE episodes</b>		
2	92(69.17%)	108(70.6%)
>2	41(30.8%)	45(29.4%)

We had observed history of overt episodic HE related to the advanced liver disease, identified on the basis of two or more episodes of overt HE in six months

beforehand the screening visit. Related patients percentages were observed in the group treated with placebo (91.2%) and rifaximin group (91.4%) who were getting lactulose at baseline, although the daily average lactulose dose was stable.

The average treatment duration observed in rifaximin group was  $128.1 \pm 45$  whereas in placebo group was  $110 \pm 61.2$  days. We also observed high compliance rate between both groups i.e., 83.2% & 84.1%. The report the breakthrough episode of HE in 15 (25%) of the patients in rifaximin group where as it is 30(50%) in placebo group. The hazard ratio was 0.39 for the breakthrough episode risk in rifaximin group in comparison to placebo group. This risk was almost 60% reduced in rifaximin in six months as compared to placebo group. The adverse event incidence was almost same in both groups i.e., 78% and 80% respectively.

## DISCUSSION

The study was planned to determine the efficacy and safety of the rifaximin drug in patients with HE. As it is the most desirable goal of any treatment in liver disease is to prevent the episode of HE<sup>1,2,4,6,7</sup>. The overt encephalopathy symptoms with decreasing self care ability; improper nutrition and no obedience to a treatment regimen may leads to severe conditions like poor quality of life and frequent hospitalization. We reported in our study that risk of breakthrough episodes of HE has been reduced due to the use of rifaximin during the time period of six months. This reduction of risk was also observed across all subgroups, which is in fact displaying the reliability of the results. This finding is confirmed by other published reports which clearly highlight the efficacy of rifaximin in treating the overt HE<sup>13-24</sup>. Our study is different from other published studies due to the examining the protective effects of rifaximin against the breakthrough episode of HE rather than its effect in treating its overt symptoms. Few of other published studies were limited to 21 days to five months<sup>14-18, 20-24</sup>. We also report in our findings that the dominance of rifaximin drug therapy over placebo and than lactulose alone also. Almost 85% of patients established concomitant lactulose through the study time, and a meaningful treatment effect was celebrated in 28 days when randomization completed. In comparison to this, a fresh single-center study of 120 patients revealed that although lactulose therapy was more operative than no active management in the hindrance of overt HE<sup>25</sup>, the treatment effects backing lactulose were outward only after 4 months. We observed in our findings that the rifaximin treatment also reduced the stay or risk of hospitalization due to HE, that intimating the

efficacy and significance of the drug. This finding also supports the findings of a chart review retrospectively<sup>4,26</sup>. This chart shows the rifaximin efficacy in comparison to lactulose and it is significantly associated to the less hospitalization stay or visits thus controlling the cost factor.

## CONCLUSIONS

We may conclude a robust protective effect of rifaximin alongside episodes of hepatic HE. It also diminishes the risk of hospitalization.

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