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Research Article

Frequency of Recurrence of Hepatic Encephalopathy in Patients Treated with Rifaximin versus PLACEBO

[1]Sadaf Ali Raja, [2]Sarwat Ali Raja and [3]Naeem Bukhari

[1]Lahore General Hospital, Lahore
[2]Associate Professor, Phd, Pharmacology & Toxicology, Lahore Pharmacy College, Lahore
[3]Associate Professor, Phd, Pharmacy Practice, Lahore Pharmacy College, Lahore

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ABSTRACT

The objective of the study was to: compare the frequency of recurrence of hepatic encephalopathy in patients treated with Rifaximin versus placebo
STUDY DESIGN: Randomized control trial
SETTING: Lahore General Hospital, Lahore
DURATION OF STUDY: APRIL 2017 TO APRIL 2018
RESULTS: Comparison of recurrence reveals in 25%(n=15) in Rifaximin Group and 51.67%(n=31) in Placebo Group while remaining 75%(n=45) in Rifaximin and 48.33%(n=29) in Placebo Group had no findings of recurrenc, p value was calculated as 0.002 which shows a significant difference in both groups.
CONCLUSION: We concluded that frequency of recurrence of hepatic encephalopathy in patients treated with rifaximin versus placebo is significantly lower in Rifaximin treated patients, however, some-other trials are required to authenticate these findings as the data is primary.

KEYWORDS: Hepatic Encephalopathy, Recurrence, Rifaximin, Placebo

INTRODUCTION

Hepatic encephalopathy is a common complication of cirrhosis.[1] In patients with cirrhosis admitted to hospital hepatic encephalopathy has been reported in 19% to 50% % of patients.[2] In 2003, more than 40,000 patients were hospitalized with hepatic encephalopathy, a number that increased to over 50,000 in 2004.[3] Although the occurrence of episodes of hepatic encephalopathy appears to be unrelated to the cause of cirrhosis,[4] increases in the frequency and severity of such episodes predict an increased risk of death.[5]

It is a severe neuropathological condition arising secondary to liver failure. The pathogenesis is not well understood; however, hyperammonemia is considered to be one causative factor.[6] The clinical manifestations of HE range from altered mental status to deep coma.[7]

The clinical diagnosis of overt hepatic encephalopathy is based on two concurrent types of symptoms: impaired mental status, as defined by the Conn score (also called West Haven criteria) (on a scale from 0 to 4, with higher scores indicating more severe impairment), and impaired neuromotor function. The Conn score is recommended by the Working Party on Hepatic Encephalopathy for

assessment of overt hepatic encephalopathy in clinical trials.[8]

Most therapies for hepatic encephalopathy focus on treating episodes as they occur and are directed at reducing the nitrogenous load in the gut, an approach that is consistent with the hypothesis that this disorder results from the systemic accumulation of gut-derived neurotoxins, especially ammonia, in patients with impaired liver function and portosystemic shunting.[9]

Rifaximin is a minimally absorbed oral antimicrobial agent that is concentrated in the gastrointestinal tract, has broad-spectrum in vitro activity against gram-positive and gram-negative aerobic and anaerobic enteric bacteria, and has a low risk of inducing bacterial resistance.[10]

In a study by Bass NM, a 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,[11] while another recent study[12] recorded hepatic encephalopathy in 42% of the patients treated with rifaximin, which shows a significant difference in efficacy of the drug and creates the need of the study.

Due to controversy that exists in literature regarding recurrence of hepatic encephalopathy in patients treated with rifixamin, we want to conduct this study again to confirm the frequency of recurrence of hepatic encephalopathy in our population so that patients may be advised and followup accordingly. Another significance of the study is that the results will be primary in Pakistan as no study with regards to this drug is conducted yet.

METHODOLOGY

In this randomized control trial a total of 120 cases (60 in each group) with liver cirrhosis both males and females (assessed clinically) and above 20 years of age with hepatic encephalopathy grade-IV were included in the study. We excluded all cases having renal failure (on lab investigations i.e RFTs), diabetes mellitus (on lab investigations) and acute fulminant hepatic failure (on lab investigations i.e LFTs). All the information about the patient was confidential. Patients were divided into two randomly assigned equal groups by using computer generated random number table. All patients were given standard treatment i.e. Lactulose 30ml 4 times a day, Bowel wash, oral Metronidazole 250mg TDS. In one group Rifaximin at dosage of 550mg twice a day for 7 days was given and compared to 2nd group on placebo i.e. 5% D/W1000cc. The recurrence (according to operational definition) of hepatic encephalopathy was recorded in both groups at 3 months followup by the researcher herself. Data analysis was done on the basis of quantitative variable like age was measured by Mean±Standard deviation. Frequency and percentages were calculated for qualitative variables like gender, and recurrence was checked in both groups. Chi-square test was used to compare recurrence of hepatic encephalopathy in both groups. P-value less than or equal to 0.05 was taken as significant.

RESULTS

A total of 120 cases(60 in each group) were enrolled to compare the frequency of recurrence of hepatic encephalopathy in patients treated with rifaximin versus placebo.

Age distribution of the patients was done which shows that 23.33%(n=14) in Rifaximin group and 28.33%(n=17) in placebo group were between 20-40 years while 76.67%(n=46) in Rifaximin Group and 71.67%(n=43) in Placebo Group were between 41-70 years of age, mean$\pm$sd was calculated as 51.58$\pm$12.22 and 52.33$\pm$12.87 years. (Table No. 1)

Gender distribution of the patients was done which shows that 55%(n=33) in Rifaximin and 48.33%(n=29) in Placebo group were male while remaining 45%(n=27) in Rifaximin and 51.67%(n=31) were females. (Table No.2)

Comparison of recurrence reveals in 25%(n=15) in Rifaximin Group and 51.67%(n=31) in Placebo Group while remaining 75%(n=45) in Rifaximin and 48.33%(n=29) in Placebo Group had no findings of recurrence, p value was

calculated as 0.002 which shows a significant difference in both groups. (Table No. 3)

TABLE No. 1: Age Distribution **(n=120)**

Age(in years)	Rifaximin Group (n=60)		Placebo Group (n=60)	
	No. of patients	%	No. of patients	%
20-40	14	23.33	17	28.33
41-70	46	76.67	43	71.67
Total	**60**	**100**	**60**	**100**

TABLE No. 2: Gender Distribution **(n=120)**

Gender	Rifaximin Group (n=60)		Placebo Group (n=60)	
	No. of patients	%	No. of patients	%
Male	33	55	29	48.33
Female	27	45	31	51.67
Total	**60**	**100**	**60**	**100**

TABLE No. 3: Comparison of Recurrence In Both Groups **(n=120)**

Recurrence	Rifaximin Group (n=60)		Placebo Group (n=60)	
	No. of patients	%	No. of patients	%
Yes	15	25	31	51.67
No	45	75	29	48.33
Total	**60**	**100**	**60**	**100**

P value=0.002

DISCUSSION

The reason behind this study was that controversy that exists in literature regarding recurrence of hepatic encephalopathy in patients treated with rifixamin, so we planned this study again to confirm the frequency of recurrence of hepatic encephalopathy in our population so that patients may be advised and followup accordingly. Another significance of the study was that the results are primary in Pakistan as no study with regards to this drug is conducted yet.

In our study, 23.33%(n=14) in Rifaximin group and 28.33%(n=17) in placebo group were between 20-40 years while 76.67%(n=46) in Rifaximin Group and 71.67%(n=43) in Placebo Group were between 41-70 years of age, mean$\pm$sd was calculated as 51.58$\pm$12.22 and 52.33$\pm$12.87 years, 55%(n=33) in Rifaximin and 48.33%(n=29) in Placebo group were male while remaining 45%(n=27) in Rifaximin and 51.67%(n=31) were females, while comparison of recurrence reveals in 25%(n=15) in Rifaximin Group and 51.67%(n=31) in Placebo Group while remaining 75%(n=45) in Rifaximin and 48.33%(n=29) in Placebo Group had no findings of recurrenc, p value was calculated as 0.002 which shows a significant difference in both groups.

The findings of our study are in agreement with a study by Bass NM, a 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[11] and in contrast with the other study[12] who recorded that thepatic encephalopathy in 42% of the patients treated with rifaximin.

Lawrence KR and colleagues[13] reviewed the effectiveness and safety of rifaximin for the treatment of hepatic encephalopathy and

recorded that Rifaximin was effective in improving behavioral, laboratory, mental status, and intellectual abnormalities associated with hepatic encephalopathy. Some studies demonstrated superior and more rapid improvement in signs or symptoms of encephalopathy during treatment with rifaximin compared with nonabsorbable disaccharides (lactulose, lactitol). Patients treated with rifaximin also required less hospitalization, had shorter duration of hospitalization, and lower hospital charges compared with lactulose-treated patients. Adverse effects of rifaximin were mostly minor gastrointestinal complaints; however, rifaximin was better tolerated than other pharmacologic treatments.

The current study differs from previous randomized studies in that it examined the protective effect of rifaximin against breakthrough episodes of hepatic encephalopathy rather than its effect in the treatment of acute. In previous randomized studies, rifaximin was administered for 21 days or less[14-18] or intermittently, for 14 or 15 days per month for 3 or 6 months.[19]

Considering the results of the current study, the hypothesis of the study that *"there is a difference in frequency of recurrence between Rifaximin and placebo"* is justified. However, these findings are primary in our setup, some other trials should be done to authenticate the findings of the current study.

CONCLUSION

- We concluded that frequency of recurrence of hepatic encephalopathy in patients treated with rifaximin versus placebo is significantly lower in Rifaximin treated patients, however, some-other trials are required to authenticate these findings as the data is primary.

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