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STUDY TO KNOW RECURRENCE OF CLINICALLY OVERT HEPATIC ENCEPHALOPATHY IN PATIENTS WITH LIVER CIRRHOSIS, RIFAXIMIN IN CONTRAST WITH PLACEBO

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Abstract

Objective: *The aim of this study is to evaluate the efficacy of Rifaximin in preventing the recurrence of overt hepatic encephalopathy in comparison to placebo in patients with recent history of overt hepatic encephalopathy two or more episodes in the past six months.*

Study Design: *Random controlled trial.*

Place and Duration of Study: *This study was conducted at the Department of Medicine, Services hospital lahore from jan 2016_ may 2017.*

Materials and Methods: *Adult patients having cirrhosis of liver and with history of two or more episodes of acute hepatic encephalopathy in the past 6 months were randomized into either the Rifaximin or placebo group. Rifaximin or placebo was given 550mg twice daily for 6 months or till the recurrence of acute attack of hepatic encephalopathy. The study participants were followed weekly for first two weeks then 2 weekly till the end of therapy. The efficacy end point was the development of breakthrough hepatic encephalopathy episode.*

Results: *A total of 96 patients were enrolled in the study after fulfilling the inclusion criteria, they were randomized into either of the two groups with 1:1ratio. Patients in the Rifaximin group had lesser recurrence of the episodes of hepatic encephalopathy (17.77%) as compared to the placebo group (37.20%) and the difference was found to be statistically significant (p value = 0.002).*

Conclusion: *This placebo controlled randomized trial has shown that the Rifaximin therapy is more effective than placebo in preventing hepatic encephalopathy recurrence.*

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INTRODUCTION:

Hepatic encephalopathy (HE) is a serious neuropsychiatric complication usually seen in decompensated chronic liver disease but can also be a feature of acute liver disease [1]. The clinical spectrum of this disease comprises of different neuropsychiatric abnormalities affecting the patient's quality of life and repeated episodes of the disease have a worse effect on the socioeconomic aspect of the patient's lives [2]. HE is broadly classified as overt and minimal. The overt HE (OHE) is a condition that encompasses the neurological and neuropsychiatric manifestations detectable at bedside by clinical tests. Whereas minimal HE (MHE) is a variant of the disease in which the patient is clinically normal and a battery of psychometric tests is used to diagnose it [3]. With cirrhosis of liver patients eventually have HE in about 50% of the patients [4]. In all the patients with one episode of OHE there is a 40% cumulative risk of OHE recurrence within 1 year and patients having recurrent bouts of OHE have a 40% risk of having another episode of OHE within 6 months even if they are on lactulose treatment [5]. Cirrhotic patients who also have Hepatic Encephalopathy have worse prognosis in contrast to the patients without HE, that is including even if the patient have same Model for End Stage Liver Disease (MELD) Score [6].

The pathogenesis of the HE is not fully understood but the role of increased ammonia in the blood is the dominant theory among others like inflammation and hyponatremia. The first and the most important step in the management of HE is the correction of the precipitating factors followed by measures to lower the ammonia levels in blood. Ammonia levels are lowered either by preventing its absorption from the gut by non- absorbable disaccharides, such as lactulose or by changing the ammonia forming flora of gut by using an antibiotic like Rifaximin [8].

In the management of HE, Rifaximin has been compared with other agents like lactulose, other antibiotics and placebo, and results showed that its effect was either same or better than other agents [10]. This study was aimed at evaluating the efficacy of Rifaximin in preventing the recurrence of OHE vs placebo in patients with recent history of OHE two or more episodes in the past six months.

MATERIALS AND METHODS:

This double blind placebo controlled randomized trial was conducted in the department of medicine, Services Hospital Lahore from jan 216_ May 2017. Cirrhotic patients secondary to any etiology, of any age and either gender who have at least two episodes of OHE in the past six months with Conn score of 2 or more were included in the study. The admitted patients with second episode of OHE in the last six months were also enrolled in the study at discharge when their episode was treated and were in remission. Patients with following conditions were excluded from the study, chronic renal insufficiency, respiratory insufficiency, electrolytes abnormalities (Serum sodium < 125mEq/L, serum Calcium > 5mEq/L, serum potassium < 2.5mEq/L), active spontaneous bacterial peritonitis, expectation of liver transplant hepatocellular carcinoma < 1 month and patients with placement of trans-jugular intrahepatic portosystemic shunt.

An informed consent of all the patients was taken. All participants were randomized simply with 1: 1 ratio into either placebo or Rifaximin group 550mg twice daily for six months or till the recurrence of OHE. Detailed history was gathered and clinical examination was performed of all patients and data recorded. The Conn score was used to establish the remission of the HE. Conn scores were defined as in the study [11]. Use of lactulose was allowed to the participants during the study period. The study participants were followed weekly for first two weeks then fortnightly till the end of therapy. Each follow up compliance checked the drug, Conn score calculated and adverse effects were noted. The efficacy end point was the development of breakthrough HE episode. SPSS version 17 was used to analyze data. Results were marginalized for gender, MELD score and history of HE. To determine the statistical difference between the two groups T-test and chi-square tests were used.

RESULTS:

A total of 96 patients were enrolled in the study after fulfilling the inclusion criteria. Random selection into both the groups with 1:1 ratio was performed. Morbidity rate was one patient in each group due to disease progression and others who we were not able to follow up. Comparison of both the groups is evident in (table 1). The study drug was stopped when the breakthrough episode of HE was documented. The study population was predominantly younger than 65 years and having hepatitis C as the most common cause of cirrhosis of liver. L actulose was used by the patients in both groups besides the study drugs.

Table No.1: Baseline characteristics of the patients according to study groups

Characteristic	Rifaximin Group (N = 45)	Placebo Group (N = 43)
Age (years)		
Mean ± SD	46.73±2.35	44.28±3.61
<65	34	36
≥ 65	11	7
Gender		
Male	24 (53.33 %)	22 (51.16%)
Female	21 (46.66%)	21 (48.83%)
No of HE episodes in the past 6 months		
2	26(57.77%)	23(53.48%)
>2	19(42.22%)	20 (46.51%)
Cause of Cirrhosis		
Hepatitis C	27 (60%)	30 (69.76%)
Hepatitis B	13 (28.88%)	11 (25.58%)
Ethanol	3 (6.66%)	1 (2.32%)
Others	2 (4.44%)	1 (2.32%)
MELD Score		
≤ 10	6 (13.33%)	4(9.30%)
10-18	25 (55.55%)	23(53.48%)
19-24	14 (31.11%)	16(37.20%)
Mean ± SD	17.52 ±3.61	15.76 ± 2.84

Breakthrough episodes of the HE were reported in 8 patients (17.77%) in Rifaximin group and 16 patients (37.20%) in placebo group (Figure 1). A statistical significance with p value of 0.002 was recorded as the difference. The ability of the Rifaximin to reduce the recurrence of HE was consistent in all the subgroups especially in patients younger than 65 years and in patients having MELD score range of 10-18, as shown in the table 2.

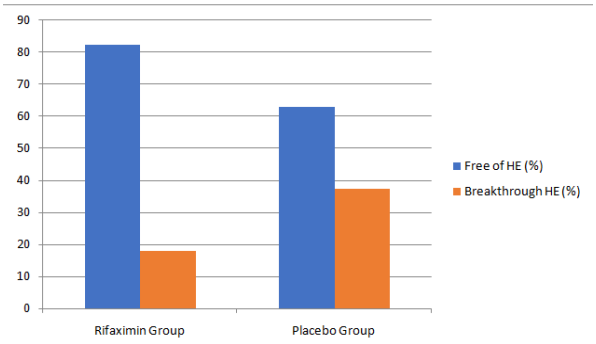

Figure No.1: Breakthrough Episodes of HE in the both Groups

The adverse events reported by the study population were similar in both the groups, Rifaximin group (53.61%) and placebo group (51.43%). The adverse events were mild including nausea, vomiting, fatigue, abdominal pain (spontaneous bacterial peritonitis was ruled out) and infections (respiratory and urinary tract infections). The study drug continued with the management of adverse events and the patients fully recovered from it.

Total of two patients died in the study population, one in each group. The patient in the Rifaximin had acute upper gastrointestinal bleed from esophageal varices, the endoscopic band ligation of the esophageal varices was done but the patient died within 18 hours of the index bleed. The patient in the placebo group had worsening of the ascites and developed type 1 hepatorenal syndrome, with serum creatinine of 4.3 mg/dl. The spontaneous bacterial peritonitis was ruled out, the patient was managed conservatively but couldn't recover.

Table No.2: Subgroup analysis of the patients free of HE

Characteristics	Rifaximin Group (n=37)	Placebo Group (n=27)	p value
Age (years)			
<65	31	20	<0.001
≥ 65	6	7	0.03
Gender			
Male	20	16	0.008
Female	17	11	0.006
MELD Score			
≤10	4	2	0.21
10-18	22	15	<0.001
19-24	11	10	0.33
No: of encepha-lopathy Episodes in the past			
2	23	17	0.006
>2	14	10	0.019

DISCUSSION:

Hepatic encephalopathy is one of the complications of the cirrhosis of liver which has a negative impact on the patient's quality of life. One of the primary objectives of the therapy in these patients is to reduce the recurrent episodes of the HE and as a result decrease the need for repeated hospitalizations and improve patient's quality of life [12,13]. The results of our study demonstrated that Rifaximin use for 6 months, in cirrhotic patients having 2 or more episodes of HE in 6 months, reduces the risk of breakthrough episode of HE. Risk of recurrence of HE was also observed within different subgroups of study population and the risk was reduced, especially

in patients who were younger than 65 and had MELD score of 10-18, further emphasizing on the importance of long term use of Rifaximin for cirrhotic patients who are in remission of HE. Different trials documented the successful response of Rifaximin in the treatment of acute OHE [14-16].

This study was different as it was conducted on cirrhotic patients when they were in remission of HE instead of patients with acute OHE. A randomized placebo controlled trial conducted in United States also checked the response of the Rifaximin in preventing the recurrence of HE and the results showed that the Rifaximin has a protective role against HE recurrence, which is consistent with our study results [10]. That study was conducted on the patients with different ethnic groups differing from our study population in many aspects including the gut flora. Rifaximin which serves as the antibiotic mainly acting through modifying the gut flora of the patients. The patients in Bass et al study were having alcohol as the predominate etiology for liver cirrhosis while in our study the most common causation for the cirrhosis was viral hepatitis either Hepatitus C or B. Despite these differences in the characteristics of the study population, both the studies concluded that Rifaximin is effective in reducing the risk of recurrence of HE. There were studies in the past which used Rifaximin for the prevention of HE but either for a shorter duration of 21 days or as an intermittent therapy of 10-15 days a month for 6 months [17-19].

A randomized open labeled trial from New Dehli, India compared lactulose with placebo for the prevention of HE and found that lactulose was effective in preventing the recurrence of HE [5]. Bacterial infections are common in decompensated cirrhotic patients and are most important precipitating factor for the development of HE [20]. Lactulose reduces the pH of the colon by the production of organic acids. This lowered pH of the colon helps the growth of acid resistant non-urease producing bacteria whereas preventing the growth of urease-producing organisms in the colon hence the ammonia production is reduced in the colonic lumen [21]. The Sharma et al trial showed that bacterial infections were reported more in the placebo arm of the study population as compared to the lactulose, signifying that lactulose helps in reducing the chances of bacterial infections in cirrhotics [20]. The addition of an antibiotic such as Rifaximin to lactulose will have a synergistic effect against the bacterial infections and prevention of the HE in patients with liver cirrhosis. As in our study the concomitant use of the lactulose was allowed to all the patients in both the groups, but lesser breakthrough episodes of the OHE occurrence in the Rifaximin group signifies that the combination of Rifaximin and lactulose is superior to the lactulose alone in the prevention of recurrent attacks of HE.

The frequency of reported general adverse events and infections were similar in both the groups (53.61% vs 51.43%). The patients fully recovered after conservative management. This was consistent with previous trials [10,22].

CONCLUSION:

The results of this randomized placebo-controlled trial show that, for patients having cirrhosis of liver with previous episodes of hepatic encephalopathy, the Rifaximin therapy is more effective than placebo in preventing hepatic encephalopathy recurrence.

Conflict of Interest: The study has no conflict of interest to declare by any author.

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