ORIGINAL ARTICLE

EFFICACY OF RIFAXIMIN IN PREVENTION OF RECURRENT HEPATIC ENCEPHALOPATHY IN LIVER CIRRHOSIS

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ABSTRACT

***Objective**: To determine the efficacy and safety of rifaximin to prevent recurrent episodes of hepatic encephalopathy in patients with liver cirrhosis as compared to lactulose alone.*

***Study Design:** Randomized controlled trial.*

***Place and Duration of Study:** Department of Gastroenterology, Shalamar Hospital, Lahore, from June 2012 to November 2014.*

***Methodology:** We randomly chose 196 Patients who did not have overt hepatic encephalopathy for approximately 4 weeks resulting from cirrhosis of liver to take rifaximin, at a dose of 550 mg twice daily (99 patients), or lactulose only (97 patients). Patients were asked to take the drug orally twice daily for 6 months or until they experience a recurrent episode of hepatic encephalopathy.*

***Results:** Rifaximin markedly decreased the risk of an episode of hepatic encephalopathy, in comparison to lactulose alone, over a six month period. A sudden episode of hepatic encephalopathy was experienced by 19 (19.19%) patients who took Rifaximin, as compared with 49 (50.51%) patients in the lactulose group. A total of 12.6% (8) of the patients in the rifaximin group were hospitalized due to hepatic encephalopathy, as compared with 23.8% (15) patients in the lactulose group. Patients who did not develop hepatic encephalopathy during study period were 79 (79.79%) out of 99 in rifaximin group and 48 (49.48%) out of 97 patients in lactulose group. Most of the patients who developed breakthrough hepatic encephalopathy had MELD score range of 21-25 in both groups. The number of mortalities and morbidities were similar in both groups.*

***Conclusion:** Over a 6 months period, treatment with rifaximin was more effective in maintaining remission from hepatic encephalopathy than lactulose alone. In our study, rifaximin significantly reduced the incidence of hospitalization due to hepatic encephalopathy.*

***Key Words:** Rifaximin, hepatic encephalopathy, cirrhosis.*

INTRODUCTION

Hepatic encephalopathy (HE) a common complication of cirrhosis, has a detrimental effect on health - related quality of life and survival.[1-4] It is the term used to explain the complex and variable changes in neuropsychiatric signs and symptoms that complicate liver disease.[4-6] Recurrent episodes of hepatic encephalopathy are debilitating, require multiple hospitalizations and make the patient incapable of performing activities of daily life.[2,5,8] The increasing number and intensity of such episodes predicts an increased risk of mortality.[1,2,7,8]

The pathogenesis of these events remains unclear.[1,2] Both hepatocellular failure and portosystemic shunting play major role in its development.[1,4,5] Gut related toxins mainly ammonia, escape hepatic detoxification and cross the blood brain barrier, ammonia is then detoxified by astrocytes.[2,7-9] The final result is the development of low-grade cerebral oedema, which eventually effects neuronal function. The goal of treatment has been to lessen the gut-derived ammonia, increased ammonia clearance and control of precipitating factors.[1-3,7-9] Lactulose has been the standard of care while oral antibiotics have been effective only to be related with toxic effects when used on long-term basis.[8-10]

Rifaximin, a synthetic antimicrobial structurally related to rifamycin has broad span of activity against gram-positive, gram-negative and anaerobic enteric bacteria and has a low risk of developing bacterial resistance.[11] systemic absorption is negligible (.4%). It is at least as effective as Lactulose and other non-absorbable antimicrobials, for example neomycin for the treatment of hepatic encephalopathy.[8,9,11]

Rifaximin has a good safety profile, better tolerated than other non-absorbable disaccharides and hence adherence to treatment may be better in longer run. In randomized studies, Rifaximin, used in addition with lactulose was found to be more effective for the prevention of frequent episodes of hepatic encephalopathy. [11,12,17]

The study population in the western world mostly consists of alcohol induced cirrhosis while in our part of the world it is mostly cirrhosis due to viral hepatitis. In addition, the micro flora in the gut in eastern population may be different from that of western population. There is a likelihood of different response to rifaximin in our population compared to the west. If it is found to be efficacious in the local population, it would help decrease the morbidity of the disease.

The aim behind this study was to evaluate the efficiency and safety of Rifaximin in the local population to avoid recurrent episodes of hepatic encephalopathy.

METHODOLOGY

This study took place at the Department of Gastroenterology, Shalamar Hospital Lahore, from June 2012 to November 2014. It was a comparative study. Patients with cirrhosis of any cause, of all ages and both gender and with a history of at least two episodes of hepatic encephalopathy in the last 6 months with a West Haven criteria of grade 0 or 1 and score of 25 or less on the model for end stage liver disease scale presenting to OPD or getting admitted to ward were included in the study. Patients admitted with hepatic encephalopathy (HE), which was precipitated by active spontaneous bacterial peritonitis (SBP), a potassium level of < 2.5 mmol/l, or intercurrent infection, gastrointestinal hemorrhage, constipation and electrolyte imbalance due to diuretic use were selected once these conditions were corrected. It was made sure, however, that this episode leading to admission was at least the second episode of HE with West Haven criteria of ≥ 2 in the past 6 months. Those patients who had known hypersensitivity to rifamycin, a calcium level > 10 mg/dl, hepatocellular carcinoma and co morbidities such as chronic kidney disease, respiratory insufficiency and cerebrovascular injury were excluded. Patients were counseled regarding the study and its implications and an informed consent was taken for participation in the study. History and clinical examination were carried out at the time of patient registration. Previous history of hepatic encephalopathy was assessed clinically with use of West Haven criteria (score 0: no abnormality detected; score 1: trivial lack of awareness, shortened attention span and anxiety; score 2: lethargy, apathy, and disorientation; score 3: somnolence, stupor, confusion: score 4: coma). MELD score was calculated.

Patients up to the mark of inclusion criteria were randomly assigned to either treatment group (Rifaximin 550 mg and Lactulose) or Lactulose only group.

Patients were requested to take the drug orally twice daily for 6 months or until they developed a sudden episode of hepatic encephalopathy or had to withdraw the drug due to some other reason. Breakthrough episode of hepatic encephalopathy was defined as West Haven criteria ≥ 2 precipitated by progression of disease, constipation or electrolyte imbalance. All enrolled patients and their attendants were informed about the possible side effects of Rifaximin and were advised to get in touch with the investigator if any new symptoms developed while on study drug. Patients developing detrimental events including intercurrent infections such as pneumonia, bacterial peritonitis or variceal hemorrhage leading to HE were asked to discontinue the study drug. Concomitant administration of Lactulose was permitted during the study.

After screening and randomization, patients were required to visit Gastroenterology-Hepatology Out-door on day 7 and every 4 weeks thereafter through 168 days. Telephonic monitoring was carried out during the week without visits to outpatients department. Safety assessments were carried out on each visit in particular infection, including infection of respiratory and gastrointestinal tract. Assessment of response to therapy on day 0 and on subsequent visits was done by West Haven criteria. The information was collected through a specifically designed performa.

Data was analyzed using Statistical Package for Social Sciences (SPSS) version 20.

RESULTS

A total of 196 patients were randomly chosen to take the study drug. Majority of patients had cirrhosis due to chronic hepatitis C. baseline characteristics were similar. A greater number of patients fell in the age group of 41 – 65 years and gender distribution in both groups was similar. Most of patients had MELD score in the range of 11 – 20 in both groups (table 1).

All enrolled patients received at least one dose of study drug and underwent at least one safety assessment after enrollment. The study medicine was stopped at the time of first sudden episode of hepatic encephalopathy or if the patients developed severe harmful events. All except 9 patients in rifaximin group and 8 patients in the other group were not using diuretics due to absence of ascites. There were however, incidences of self-medication with metronidazole and ciprofloxacin/ levofloxacin for uninvestigated episodes of either diarrhea, abdominal pain or cough productive of sputum by 16 patients in Rifaximin group and 12 patients in Lactulose group. All enrolled patients were adherent to the use of study

drug and the follow-up visits to gastroenterology outdoor except for one patient in each group who was lost to follow-up. Breakthrough episodes were reported in 19 (19.19%) of 99 patients in treatment group and 49 (50.51%) of 97 patients in Lactulose group. The difference turned out to be significant with a p-value of< 0.001 (table III). There is a relative decrease in the risk of a break through episodes by 57% with rifaximin in comparison with lactulose group during the 6-months study periods.

Most common cause of HE in both groups was progression of disease (Table 4). There are 16 patients in both groups, who were investigated for all known precipitating causes of hepatic encephalopathy and none were found. An average rise of MELD score by 9 in Lactulose group and 6 in rifaximin group was noted when these patients presented with PSE during the study. A total of 8 (12.6%) patients in the Rifaximin group were admitted in the hospital involving hepatic encephalopathy as compared with 15 (23.8%) patients in lactulose group. There is a reduction of 48% with rifaximin as compared with lactulose group hepatic encephalopathy, as compared with 15 (23.8%) patients in the risk of hospitalization.

The incidence of harmful events reported during the study was similar in both groups. Study drug was discontinued once severe detrimental events were reported. Most adverse events were either due to progression of disease or complications of cirrhosis and were managed along lines of prescribed standard of care (table 4). The symptoms of nausea/vomiting, generalized weakness, sore throat and fatigue resolved once study drug was discontinued. The patients in treatment group who developed abdominal pain were investigated for SBP and no such evidence was found on ascitic fluid analysis. Abdominal pain resolved on discontinuation of study drug.

One patient in treatment group who died of acute on chronic hepatitis had a baseline bilirubin of 1.9 mg/dl which rose to 15.9 mg/dl and MELD rose from 16 to 34 in Lactulose group, acute on chronic hepatitis was precipitated by hepatitis E. He was asked to discontinue the study medicine and was managed on lines of prescribed standard of care. There were 14 deaths during the study. Seven patients died in Treatment group and 7 in Placebo group. Most of the deaths were related either to progression of disease or secondary to infection (Table 4). All patients had at baseline, apart from hepatic encephalopathy, one or more signs of decompensated cirrhosis i.e. ascites, edema or history of variceal bleed.

Table 1: *Basic Demographics.*

	Lactulose Group (n = 97)	**Rifaximin Group (n = 99)**
Age in years		
<50	60	66
≥50	37	33
Mean ± SD	44.45 ±3.43	43.97 ± 3.54
Gender		
Male	47 (48.45%)	46 (46.46%)
Female	50 (51.54%)	53 (53.53%)
Range of MELD score		
0 - 10	8 (8.24%)	9 (9.09%)
11 - 20	51 (52.57%)	49 (49%)
21 - 25	38 (39.17%)	41 (41.41%)
Mean ± SD	17.74 ± 2.98	15.45 ± 3.45
Number of episodes of encephalopathy in the past		
2 episodes	45 (46.39%)	51 (51.51%)
> 2 episodes	52 (53.60%)	48 (48.48%)
Etiology of cirrhosis		
Hepatitis C	88 (90.72%)	87 (87.87%)
Hepatitis B	6 (6.18%)	5 (5.05%)
Ethanol	2 (2.06%)	3 (3.03%)
Other	1 (1.03%)	2 (2.02%)

MELD = Model for End Stage Liver Disease

Table 2: *Subgroup analysis of patients free of PSE during trial.*

	Lactulose Group 48 (49.48%)	Rifaximin Group 79 (79.79%)	p-value
Age (in years)			
< 50	36 (75%)	58 (73.41%)	0.833
≥ 50	11 (25%)	21 (26.5%)	
GENDER			
Male	22 (45.83%)	37 (46.83%)	0.913
Female	26 (54.17%)	42 (53.16%)	
Range of MELD score			
0 – 10	6 (12.5%)	6 (7.59%)	0.633
11 – 20	37 (77.08%)	63 (79.74%)	
21 – 25	5 (10.41%)	10 (12.65%)	
Number of episodes of encephalopathy in the past			0.275
2	21 (43.75%)	43 (54.43%)	
> 2	27 (56.25%)	36 (45.56%)	

Table 3: *Subgroup analysis of patients with breakthrough PSE.*

Total	Control Group 49 (50.51%)	Treatment Group 19 (19.19%)	p-value < 0.001
Age (in years)			
	49	19	0.418
< 50	25 (51.02%)	07 (36.84%)	Insignificant
≥ 50	24 (48.97%)	12 (63.15%)	
Gender			
Male	21 (42.85%)	11 (57.85%)	0.270
Female	28 (57.14%)	07 (42.10%)	Insignificant
Range of MELD score			
0 – 10	1 (2.04%)	0	0.290
11 – 20	16 (32.65%)	3 (15.78%)	Insignificant
21 – 25	32 (65.30%)	16 (84.21%)	
Number of episodes of encephalopathy in the past			0.118
2	9 (18.38%)	07 (36.84%)	Insignificant
> 2	41 (83.67%)	12 (63.15%)	

DISCUSSION

To prevent hepatic encephalopathy is an important aim in the treatment of patients with liver ailment,[1,2,4,6,7] especially since symptoms of overt encephalopathy are associated with great morbidity and noncompliance to a therapeutic regimen, which in turn leads to repeated hospitalizations, and a poor quality of life.[1-4,12,14,15,18] Our study showed that rifaximin reduced the risk of a sudden episode of hepatic encephalopathy during the time period of 6-month among patients in remission who had a recent history of frequent overt hepatic encephalopathy (≥ 2 episodes within the previous 6 months) before enrollment. Our study shows the superiority of rifaximin treatment over lactulose therapy alone. More than 90% of patients also received concomitant lactulose during the study period, and a significant treatment effect was noted within 28 days after randomization. In contrast, a recent local study of 126 patients showed that rifaximin treatment has no role in the avoidance of frequent hepatic encephalopathy.[17]

In our study, rifaximin therapy decreased the risk of hospitalization secondary to hepatic encephalopathy, depicting the clinical significance of our efficacy findings. Also, the reduced risk of hospitalization means lower hospital costs.[26,27,28,30]

The incidences of adverse events were same in the rifaximin group and the lactulose group. The safety

Table 4: *Cause of PSE and adverse events and deaths.*

Causes of PSE	Control Group	Treatments Group
Constipation	11	8
Sepsis due to pneumonia	3	2
Hypokalemia due to overdiuresis	11	7
Progression of disease	21	15
SBP	8	6
SBP + HRS	3	3 (5.88%)
Variceal bleed	9	4
Acute on chronic hepatitis	6	3
Adverse events / deaths	-	-
Death due to persistent PSE	2 (18.18%)	1 (7.69%)
Death due to HRS	2 (18.18%)	2 (15.38%)
Death due to acute on chronic hepatitis	-	1 (7.69%)
Death due to pneumonia	1(9.09%)	1 (7.69%)
Death due to cellulitis	1(9.09%)	-
Death due to variceal bleed	1(9.09%)	2 (15.83%)
Abdominal pain	-	1 (7.69%)
Nausea and vomiting	2 (18.18%)	3 (23.08%)
Sore throat / fatigue	1(9.09%)	-
Gen. weakness	-	1 (7.69%)
Missing data	1(9.09%)	1 (7.69%)
Self – medication with other antibiotics	10/63 (15.8%)	4/63 (6.3%)

SBP = Spontaneous Bacterial Peritonitis; HRS = Hepato Renal Syndrome; PSE = Portosystemic encephalopathy.

profile of rifaximin appears to be superior to that of systemic antibiotics, particularly for patients with liver ailment.[29,30] The nephrotoxicity and ototoxicity associated with the use of aminoglycosides (e.g., neomycin and paromomycins), nausea and peripheral neuropathy with prolonged use of metronidazole minimizes their use in patients with advanced hepatocellular disease.[19,21,and22]

The risk of bacterial resistance appears to be lower with rifaximin than with systemic antibiotics because plasma levels of rifaximin are miminal.[23,24,and25] In addition, whereas resistance to other antimicrobial agents is plasmid-mediated, resistance to rifaximin is carried out through reversible genomic change. Both in vitro and in vivo studies of the effects of rifaximin on commensal flora describes that Rifaximin resistant organisms have low viability.[19,21,30].

In summary, this study shows a significant protective effect of rifaximin against episodes of hepatic encephalopathy. Rifaximin also decreases the risk of hospitalization involving hepatic encephalopathy.

CONCLUSION

Over a 6-month period, treatment with Rifaximin maintained remission from hepatic encephalopathy more efficiently than did lactulose. Rifaximin treatment also significantly reduced the risk of hospitalization involving hepatic encephalopathy.

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