

## Original Article

# Comparison efficacy of Rifaximin plus Lactulose vs. Lactulose alone in treating Hepatic Encephalopathy

Tanveer Hussain<sup>1</sup>, Misbah Sattar<sup>2</sup>, Sara Mustafa<sup>3</sup>, Uzma Batool<sup>4</sup>, Shafqat Iqbal<sup>5</sup>, Binish Hassan<sup>6</sup>

<sup>1</sup> Assistant Professor, Department of Gastroenterology, Holy Family Hospital, Rawalpindi.

<sup>2</sup> Post-graduate Trainee, Department of Gastroenterology, Holy Family Hospital, Rawalpindi.

<sup>3</sup> Senior Registrar, Benazir Bhutto Hospital, Rawalpindi.

<sup>4</sup> Senior Registrar, Benazir Bhutto Hospital, Rawalpindi.

<sup>5</sup> Medical Officer, Holy Family Hospital, Rawalpindi.

<sup>6</sup> Post-graduate Trainee, Department of Gastroenterology, Holy Family Hospital, Rawalpindi.

## Author's Contribution

<sup>1,2</sup> Conception of study

<sup>2,4,5,6</sup> Experimentation/Study conduction

<sup>1,2</sup> Analysis/Interpretation/Discussion

<sup>1,3</sup> Manuscript Writing

<sup>1</sup> Critical Review

<sup>2,4,5,6</sup> Facilitation and Material analysis

## Corresponding Author

Dr. Tanveer Hussain,

Assistant Professor,

Department of Gastroenterology,

Holy Family Hospital,

Rawalpindi

Email: drtanveer@hotmail.com

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## Abstract

**Introduction:** Hepatic Encephalopathy is a syndrome observed in patients with liver cirrhosis. Various treatment modalities are in use for the treatment of Porto Systemic Encephalopathy (PSE). Our study aimed to compare the efficacy of Rifaximin plus Lactulose vs. Lactulose alone in the treatment of Hepatic Encephalopathy in the local population.

**Material and Methods:** The study was conducted at a tertiary care hospital recruiting decompensated chronic liver disease (DCLD) patients with PSE. Using simple random sampling, patients were divided into two groups (A & B). Patients in group A received Lactulose plus Rifaximin while group B received Lactulose alone. Efficacy of treatment was assessed as the return of the conscious level to pre-encephalopathy state as per clinical examination within 1 week after initiation of the treatment.

**Results:** A total of 124 patients were included in the study with each group (A & B) containing 62 patients. Frequency and percentage of efficacy among group A (Rifaximin plus Lactulose) versus group B (Lactulose alone) in treating Hepatic encephalopathy was 45 (72.6%) and 32 (51.6%) respectively.

**Conclusion:** The study concluded that there is a significant difference in proportions of patients showing complete recovery from Hepatic encephalopathy treated with Lactulose plus Rifaximin as compared to Lactulose alone.

**Keywords:** Liver Cirrhosis, Hepatic Encephalopathy, Rifaximin.

## Introduction

Liver cirrhosis is the final common pathological pathway of liver damage arising from a wide variety of chronic liver diseases. The aetiology of cirrhosis varies geographically with Alcoholic liver disease, Chronic Hepatitis C Virus (HCV) infection, and non-alcoholic fatty liver disease (NAFLD) being the most common causes in western countries, whereas chronic hepatitis B and C are the primary cause of liver cirrhosis in the Asia-Pacific region.<sup>1,2</sup>

Liver cirrhosis is associated with a number of complications that can even lead to mortality but the most common complication is portosystemic encephalopathy that results in significant mortality.<sup>3</sup> Hepatic encephalopathy is defined as a spectrum of neuropsychiatric abnormalities in patients with liver dysfunction, after exclusion of other known brain diseases. The development of hepatic encephalopathy is explained, to some extent, by the effect of neurotoxic substances, which occurs in the setting of cirrhosis and portal hypertension.<sup>4</sup> The development of hepatic encephalopathy negatively impacts patient survival. The occurrence of encephalopathy leads to hospitalization is associated with a survival probability of 42% at 1-year and 23% at 3 years. Hepatic encephalopathy is also the most common, possibly preventable, cause for readmission.<sup>5</sup>

Ammonia produced in the gut mainly by the colonic bacteria is the most important neurotoxic substance involved in the pathogenesis of PSE.<sup>4</sup> Lactulose decreases the ammonia levels by increasing its release from the gut by decreasing the transit time of gut, decreases production and increased consumption of ammonia in the gut by acting on various groups of colonic bacteria.<sup>6</sup>

Rifaximin also helps PSE by having a bactericidal effect on ammonia producing gut flora.<sup>7</sup> The rationale of this study was to assess the efficacy of lactulose alone vs. in combination with Rifaximin for the treatment of PSE.

## Materials and Methods

After approval from the ethical review committee, a randomized controlled trial was conducted in the Gastroenterology Department of Holy Family Hospital Rawalpindi for 6 months from 16<sup>th</sup> of March 2019 to 15<sup>th</sup> of September 2019 in patients of both sex groups with ages in the range of 20-70 years suffering from hepatic encephalopathy. Patients with liver cirrhosis

who presented with symptoms ranging from irritability and confused state to coma as per clinical examination (>6 hours) were labeled to have hepatic encephalopathy and its grade (I-IV) was categorized on West Heaven Criteria of hepatic encephalopathy.<sup>8</sup> Patients with renal impairment (serum creatinine>1.5 mg/dl), or having space-occupying lesion of the liver (on abdominal ultrasound), serum sodium<120 mmol/l as per investigations, patients allergic to Rifaximin and patients with stroke (on CT scan), CNS infection, history of fits or anti-psychiatric medications were excluded.

Written informed consent was taken from the first relatives of the patients. After a brief history and confirmation of diagnosis, patients were stratified into either group A or B. Group A patients received Lactulose plus Rifaximin while group B received Lactulose alone. The enrollment in study groups was made through randomization through the lottery method.

Group A received Tab Rifaximin 550 mg twice a day and Lactulose 30 ml thrice a day so that patients pass at least 2 semi-soft stools per day. Patients in group B were treated with lactulose 30ml three times a day. Patients were managed and monitored as per standard treatment protocols for the management of hepatic encephalopathy. All relevant investigations were carried out to classify patients for the CTP score. All the patients had received medication from the same pharmaceutical company to eliminate bias and confounding variables were controlled by exclusion. The primary outcome measure was a complete reversal of the conscious level to pre- encephalopathy state. Patients were given treatment until complete recovery or a maximum of seven days of treatment. Patients not responding to treatment after seven days were considered as treatment failures.

All the data was noted and recorded on Performa which contained patients' demographic and clinical information. The grade of the hepatic encephalopathy and efficacy of the treatment was presented as frequency and percentage. Chi-square test was applied for comparison of the efficacy of the treatment between the two groups taking a *p*-value of  $\leq 0.05$  as statistically significant.

Data was entered and analyzed in SPSS version 21.0

## Results

A total of 124 patients were included according to the inclusion criteria of the study. The mean age of the population was  $45.18 \pm 15.20$  years. There were 69

(55.6%) male and 55 (44.4%) female patients. Patients were divided into two groups. Group A patients received Lactulose plus Rifaximin while group B received Lactulose alone.

Grades of hepatic encephalopathy on presentation assessed in terms of frequency and percentage. 46 (37.1%) patients were presented with grade IV hepatic encephalopathy and 43 (34.7%) patients with grade III hepatic encephalopathy. This is illustrated in Table 1.

**Table 1: Frequency & percentage of Grade of Hepatic Encephalopathy among both groups at the time of admission**

		Two Groups		Total
		Group A	Group B	
Grade of Hepatic Encephalopathy on presentation	Grade I	7 11.3%	3 4.8%	10 8.1%
	Grade II	12 19.4%	13 21.0%	25 20.2%
	Grade III	21 33.9%	22 35.5%	43 34.7%
	Grade IV	22 35.5%	24 38.7%	46 37.1%
Total		62 100.0 %	62 100.0 %	124 100.0 %

The purpose of the study was to compare the efficacy of Rifaximin plus Lactulose versus Lactulose alone in treating patients with hepatic encephalopathy. The frequency and percentage of efficacy with Rifaximin plus Lactulose vs Lactulose alone was 45 (72.6%) and 32 (51.6%) respectively, as shown in Table 2. The chi-square test showed a significant difference between the two groups ( $P=0.016$ ). Therefore we recommend that a combination of Lactulose and Rifaximin as compared to lactulose alone is a much better treatment modality for patients with hepatic encephalopathy.

**Table 2: Comparison of efficacy between two groups(A and B)**

		Two Groups		Total
		Group A	Group B	
Efficacy	Yes	45 72.6%	32 51.6%	77 62.1%
	No	17 27.4%	30 48.4%	47 37.9%
Total		62	62	124

Effect modifiers on treatment like age, gender, and grade of hepatic encephalopathy were compared with the efficacy of the two groups that revealed a statistically significant efficacy of Lactulose and Rifaximin in the age group 20-40, male patients and hepatic encephalopathy grade. This is shown in Tables 3, 4, and 5.

**Table 3: Effect modifier like Age stratification with the comparison of Efficacy of among both groups**

Age Groups	Efficacy	Two Groups		Total	P-Value
		Group A	Group B		
20 - 40 years	Yes	23 79.3%	10 45.5%	33 64.7	0.012
	No	6 20.7%	12 54.5%	18 35.3%	
41 - 70 years	Yes	22 66.7%	22 55.0%	44 60.3%	0.311
	No	11 33.3%	18 45.0%	29 39.7%	

**Table 4: Effect modifier like Gender stratification with the comparison of Efficacy of among both groups**

Gender	Efficacy	Two Groups		Total	P-Value
		Group A	Group B		
Male	Yes	22 75.9%	21 52.5%	43 62.3%	0.058
	No	7 24.1%	19 47.5%	26 37.7%	
Female	Yes	23 69.7%	11 50.0%	34 61.8%	0.308
	No	10 30.3%	11 50.0%	21 38.2%	

**Table 5: Effect modifier like Grade of Hepatic Encephalopathy stratification with the comparison of Efficacy of among both groups**

Grade of Hepatic Encephalopathy	Efficacy	Two Groups		Total	P-Value
		Group A	Group B		
Grade I	Yes	6 85.7%	2 66.7%	8 80.0%	0.490
	No	1 14.3%	1 33.3%	2 20.0%	
Grade II	Yes	9 66.7%	6 42.2%	14 56.0%	0.302
	No	4 33.3%	7 53.8%	11 44.0%	
Grade III	Yes	15 71.4%	10 45.5%	25 58.1%	0.084
	No	6 28.6%	12 54.5%	18 41.9%	
Grade IV	Yes	16 72.7%	14 58.3%	30 65.2%	0.306
	No	6 27.3%	10 41.7%	16 34.8%	

## Discussion

Hepatic encephalopathy is a serious but potentially reversible disorder with a wide spectrum of neuropsychiatric abnormalities and motor disturbances that range from mild alteration of cognitive and motor function to coma and death. It is a challenging complication of advanced liver disease and is estimated to occur in 30 to 45% of patients with liver cirrhosis and 10–50% of patients with Trans-jugular intrahepatic Porto-systemic shunts.<sup>10</sup> The survival probability is 42 % at 1 year of follow-up and 23% at 3 years in patients with cirrhosis with the first episode of hepatic encephalopathy.<sup>11</sup> The primary treatment is the identification and treatment of the precipitating factors. The majority of the drugs used in the treatment of hepatic encephalopathy are primarily directed at the reduction or elimination of the increased neurotoxic ammonia levels. Lactulose, a non-absorbable disaccharide, remains the mainstay treatment for PSE. Despite the widespread use of Lactulose, evidence supporting its efficacy for the treatment of hepatic encephalopathy is limited. A systematic review of the literature found lactulose to be more effective than placebo in improving encephalopathy, but with no effect on mortality.<sup>12</sup> However, when only the highest-quality studies were included, no significant effect on the improvement of

hepatic encephalopathy was seen with Lactulose therapy.

Rifaximin, a semisynthetic derivative of Rifamycin, is minimally absorbed. It 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. No dosage adjustments are necessary for patients with liver dysfunction or renal insufficiency.<sup>13</sup> With minimal systemic bioavailability, Rifaximin may be more conducive to long-term use than other, more bioavailable antibiotics with detrimental side effects. It has been proven to prevent the episode of hepatic encephalopathy and decrease the risk of hospitalization. In randomized studies, Rifaximin was more effective than non-absorbable disaccharides and had efficacy that was equivalent to or greater than that of other antibiotics used in the treatment of acute hepatic encephalopathy.<sup>12</sup> In a recent meta-analysis, Rifaximin is as effective as other conventional oral agents for the treatment of hepatic encephalopathy with a better safety profile. There is a paucity of data on the evaluation of a combination of Rifaximin plus Lactulose in the treatment of hepatic encephalopathy.<sup>13</sup> In our study, the mean age (years) was  $45.18 \pm 15.20$ . In this study, the majority of the patients 46 (37.1%) were presented with grade IV of hepatic encephalopathy, following by 43 (34.7%) patients of grade III hepatic encephalopathy. These results are

quite comparable with previous studies.<sup>9</sup> In our study, the percentage of efficacy among Rifaximin plus Lactulose vs. Lactulose alone for the treatment of hepatic encephalopathy was 72.6% and 51.6% respectively. Likewise, Sharma et al in 2013 conducted a study and found that the efficacy of Lactulose plus Rifaximin was 76% vs. Lactulose alone 44% showed complete reversal of hepatic encephalopathy.<sup>9</sup> In light of our results and comparison with previous studies management plan of hepatic encephalopathy should consist of Lactulose plus Rifaximin rather than Lactulose alone if there are no contraindications for a better clinical outcome.

## Conclusion

The study concluded that there is a significant difference in proportions of patients getting complete recovery from hepatic encephalopathy treated with Lactulose plus Rifaximin as compared to Lactulose alone. The combination is more efficacious than Lactulose alone. However, further studies at different centers can be conducted to reach concrete evidence of optimizing the better treatment modality for the patients suffering from Hepatic Encephalopathy and its correlation with mortality.

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