

# Comparison of Dual Therapy, Rifaximin plus Lactulose with Monotherapy, Lactulose Alone in the Treatment of Portosystemic Encephalopathy

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## ABSTRACT

**Objective:** To compare the efficacy of dual therapy (rifaximin and lactulose) and lactulose monotherapy in the treatment of porto-systemic encephalopathy.

**Study Design:** Randomized control trial.

**Place and Duration of Study:** Department of Gastroenterology, PIMS Hospital, Islamabad from 1<sup>st</sup> July 2020 to 31<sup>st</sup> December 2020.

**Methodology:** One hundred and fifty patients of both genders age ranges from 18-65 years with liver cirrhosis having hepatic encephalopathy grade II or above were included. They were divided in two groups; each group comprised 75 patients. Group A took lactulose and rifaximin, while lactulose alone was given to Group B. All patients were monitored for 5 days on the basis of Child Pugh Criteria.

**Results:** The mean age was 40.02+24.4 years. One hundred twenty six (85.1%) of patients were above 50 years. Males were 60%, majority of patients were from the emergency department, while 17 were from OPD. HCV was identified as the major cause of cirrhosis (72.6%), while HBV (14.6%), alcohol (4%) and others (8.6%) contributed nominally. Constipation was major precipitating factor in 83 patients while sepsis and UGI Bleed was culprit in 31 and 19 patients respectively. Sixty patients (80%) of group A of both genders showed improvement in five days, while 42 patients (56%) of group B showed improvement in the same period of time ( $p=0.006$ ). It was found more in males and elder patients.

**Practical implication:** Dual therapy will reduce the morbidity, hospital stay and cost of treatment. It may also help in making local guidelines for treatment of hepatic encephalopathy.

**Conclusion:** Rifaximin plus lactulose therapy was far superior to lactulose monotherapy in every age group and either gender.

**Keywords:** Porto systemic encephalopathy, Decompensated chronic liver disease, Rifaximin lactulose therapy, Lactulose monotherapy

## INTRODUCTION

Hepatic encephalopathy is an important issue of Chronic liver disease and is anticipated to affect around 20% patients with decompensated liver disease yearly.<sup>1</sup> A recent study carried out in Pakistan showed the frequency of hepatic encephalopathy (HE) in cirrhotic patients is more than 60%.<sup>2</sup> It varies from altered sleep pattern, confusion and drowsiness to coma and eventually death but it is fully reversible with proper therapy.<sup>3</sup> The treatment of HE includes identifying the potential precipitating event and managing it accordingly. As various studies have elucidated that ammonia has a key role in the development of hepatic encephalopathy<sup>4</sup>, medicine like lactulose, a non-absorbable disaccharide is the essential drug for not only the treatment but also for secondary prevention of HE.<sup>5</sup>

Rifaximin is derived from rifamycin and is commonly used in *C. difficile* infection, traveller's diarrhea, hepatic Encephalopathy and irritable bowel syndrome. A very important benefit of using rifaximin is that its dose does not need to be adjusted in patients with renal and hepatic impairment.<sup>6,7</sup> Its role has been established in preventing hepatic encephalopathy and in decreasing the risk of admission to the hospital.<sup>8</sup> In various randomized controlled studies, rifaximin has been proved more helpful than non-absorbable lactulose and had effectiveness equal or more than other antibiotics which were used in the management of portosystemic encephalopathy.<sup>9-12</sup> The rifaximin add on therapy to lactulose is more promising in the management of HE. Not only there is difference in effectiveness rather dual therapy also reduces the length of hospitalization in contrast with lactulose monotherapy.<sup>13</sup>

There is not much local data available on the rifaximin and lactulose combination therapy in the management of HE. The current study will allow comparison of the safety and effectiveness of combination therapy vs monotherapy in the treatment of overt HE. It may also help in making local guidelines for treatment of hepatic encephalopathy.

## MATERIALS AND METHODS

This randomized controlled study was conducted at Department of Gastroenterology, PIMS Hospital, Islamabad from 1<sup>st</sup> July 2020 to 31<sup>st</sup> December 2020 and 150 patients of either sex having aged 18-65 years with PSE Grade II and above brought in Gastroenterology OPD or Emergency Department were included. Approval was taken from the ethical committee. History and thorough examination were performed of all the patients. Those who had some degenerative CNS disease or major psychiatric illness, HCC, creatinine more than 1.5 or active alcohol intake in last less than 4 weeks before admission were excluded from the study. After establishing the clinical diagnosis of Hepatic Encephalopathy and grading of OHE, patients were distributed into two groups (75 each): group A or B by the lottery method. Group A patients were treated with dual therapy rifaximin and lactulose (R+L) along with the standard treatment with the following doses. Rifaximin: 550 mg capsule twice a day and lactulose, 30 ml thrice a day, with the target 2-3 stools in a day. In Group B lactulose (L) 30-60 ml and a placebo capsule were given thrice a day along with the standard treatment with the similar target of 2-3 stools in a day. The rest of the standard treatments were the same in both groups. Monitoring of each patient was done for 5 days. The patients were followed-up until their discharge or death during hospitalization. The data was entered analyzed through SPSS-20. Chi-square test was applied to analyze the viability of both drugs. P value less than 0.05 was considered statistically significant.

## RESULTS

The mean age of study patients was 40.02+24.4 years ranging from 18 to 65 years. Almost 51.4% of patients were above 50 years of age while about 32.7% were above 60 years of age. Males were 60%, majority of patients were from the emergency department, while 17 were from OPD (Table 1). HCV was identified as the major cause of cirrhosis (72.6%), while HBV (14.6%), alcohol (4%) and others (8.6%) contributed nominally. In

addition, constipation was a precipitating factor in 83 patients, sepsis 31, UGI Bleed 19 and electrolyte imbalance were present in 15 of the study cases (Table 2). In Group A, 35 (76%) male patients responded to R+L therapy while 11 (23.91%) male patients had no response to R + L therapy.

Table 1: Demographic information of the patients (n=150)

Variable	No.	%
Age (years)		
18 – 30	4	2.6
31 – 40	4	2.6
41 – 50	16	10.7
51 – 60	77	51.4
> 60	49	32.7
Gender		
Male	90	60.0
Female	60	40.0
Mode of presentation		
Emergency	133	88.6
Outpatient	17	11.4

In Group B, we found out that 25 (56.8%) male patients responded to lactulose based standard therapy while 19 (43.1%) male

Table 3: Stratification according to gender

Gender	Rifaximin plus Lactulose		Lactulose Monotherapy		P value
	Yes	No	Yes	No	
Males (n=90)	46 (51.11%)		44 (48.88%)		0.8633
Male (improvement in grades of hepatic encephalopathy)	37 (80.43%)	9 (19.56%)	25 (56.8%)	19 (43.18%)	0.0156
Females (n = 60)	29 (48.33%)		31 (51.66%)		0.833
Female (improvement in grades of hepatic encephalopathy)	23 (79.31%)	6 (20.68%)	17 (55.83%)	14 (45.16%)	0.04

## DISCUSSION

At present treatment options for HE includes antibiotics and non-absorbable disaccharides which decrease the level of ammonia. Lactulose is the considered first-line drug for the treatment of HE.<sup>5</sup> Rifaximin role as a supportive therapy to lactulose in the management of OHE is observed in many studies which can improve the empiric treatment and help in reducing the hospitalizations and economic burden. To see the results of combination therapy in our population this study was carried out. We observed that R+L therapy was more effective than lactulose alone in the treatment of OHE in all age and gender groups. Though there are very limited studies on this topic but the available data support efficacy of combination therapy. Almost same results were found in an Indian study where the response rate was 76% in the combination therapy group (rifaximin plus lactulose) while fifty percent was the response rate in Group B lactulose only.<sup>13</sup>

Male gender was predominant in our sample with a 60 % proportion and a 1.5:1 ratio of male to female. Previous research from India was also consistent with these results, with the majority of male patients having OHE (6.5:1 and 2.8:1 respectively).<sup>13,15</sup> Though not our primary objective, we associated the incidence of HE with gender and age groups in the study. There was an increasing trend of cirrhosis and hence HE with aging. Also, there was a clear indication that males were more likely to have HE with 90 (60%) cases out of the total 150 studied cases.

The aetiology of cirrhosis in our study patients was HCV (72.6%), HBV (14.6%), Alcohol (4%) and others (8%) cases. In a Local study carried out in Holy Family Hospital Rawalpindi, Pakistan DCLD was associated with HCV in 97 % of cases, HBV (1.5%), cryptogenic (1.5%) and Alcohol (0.5%).<sup>16</sup> Another study carried out in Khyber teaching hospital also showed similar results with HCV as a cause of DCLD at 61.8%, HBV at 18%, Both HBV and HCV at 5.3%, both HBV and Anti-HDV 4.2 %, Alcohol at 3.2%, PBC 2%, Wilsons (1.05%), hemochromatosis (1.05%) and no cause found in 3.15%.<sup>17</sup> So the major cause of Cirrhosis in our part of the world is HCV as compared to Western world where alcohol is commonly used. We found that the major precipitating factor of HE in the present study was constipation (56.6%). Other factors were sepsis (20.6%), UGI bleed (12.6%) and electrolyte imbalance

patients had no response to lactulose therapy. In females, we found out that in Group A (R+L therapy) 21 (72.4%) female patients responded while 8 (27.5%) female patients had no response. In Group B, (lactulose-based therapy) we found out that 18 (58%) female patients responded while 13 (41.9%) female patients had no response to lactulose-based standard therapy. Furthermore, a variation in response rate, with respect to age, was also observed (Table 3).

Table 2: Aetiology of DCLD and precipitating factor of HE

Aetiology	Group A		Group B	
	No.	%	No.	%
HCV	57	38.0	52	34.6
HBV	12	8.0	10	6.6
Alcohol	2	1.4	4	2.7
Others	7	4.7	6	4.0
Constipation	44	29.4	41	27.4
Sepsis	16	10.7	15	10.0
UGI Bleed	11	7.4	8	5.4
Electrolyte imbalance	9	6.0	6	4.0

(10 %). On the other hand, a study carried out at Agha Khan Hospital, Karachi Pakistan showed SBP as the most common precipitant (20.5%) but still the second most common and significant factor was constipation (18.3%).<sup>18</sup> In a recent study performed in Shariati Hospital, Tehran province, Iran to compare the effectiveness of L plus PEG with L alone in the management of HE, the most common precipitating factor was UGI bleeding 45% (18 out of 40 patients) seconded by constipation 15 out of 40 patients (37.5%).<sup>19</sup> So, constipation is an important precipitating factor of HE which can be prevented by proper education of the patient at the time of discharge and compliance to medication.

So the results of this study direct to conduct further similar studies and also support the idea of making rifaximin with lactulose part of the standard treatment of OHE. However, there were a few limitations of the study as well, which are mainly related to limited study parameters. Also, there were different aetiologies of DCLD in the selected patients and different child classes. Moreover, the patients were not followed up for a longer duration due to the time constraints of the study period and continuing rifaximin after discharge for longer durations is not economical for patients.

## CONCLUSION

Rifaximin plus lactulose combination therapy is far superior to lactulose monotherapy (78.66% vs. 57.33%) in the management of Overt HE in all ages and genders.

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