

# A comparative study to determine the short-term mortality and clinical improvement in hepatic encephalopathy using either rifaximin and or lactulose



Uttam Biswas<sup>1</sup>, Shyamal Kanti Pal<sup>1</sup>, Pallabi Ray Chaudhuri<sup>2</sup>, Debanjan Roychowdhury<sup>3</sup>, Abhranil Dhar<sup>3</sup>, Anirudhda Roy<sup>4</sup>

<sup>1</sup>Assistant Professor, <sup>3</sup>Junior Resident, Department of Medicine, Burdwan Medical College and Hospital, Purba Burdwan, West-Bengal, India, <sup>2</sup>Senior Resident, Department of Ophthalmology, Dr. B N Bose State General Hospital, North 24 Paraganas, West Bengal, India, <sup>4</sup>Professor, Department of Medicine, R.G.Kar Medical College & Hospital, Kolkata, West Bengal, India

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## ABSTRACT

**Background:** Hepatic encephalopathy can be reversed by correcting precipitating factors and efficiently managed by lactulose and or rifaximin. **Aims and Objective:** The aim of this study to compare the effectiveness of three different modes of treatment in our study populations. **Materials and Methods:** Ninety patients of decompensated chronic liver diseases were selected and randomised to treat with either lactulose or rifaximin or both lactulose and rifaximin (30 patients in each group) for 7 days. Clinical outcome and short term mortality were noted in each group of treatment. This study was to review the comparison of the effectiveness of Rifaximin (1200mg/day, in 3 divided doses) alone or in combination with Lactulose (60gram/day, in divided doses) or Lactulose (60gram/day) alone to reduce the short term mortality and clinical improvement in hepatic encephalopathy of any grade of any cause in adult (> 18 years) admitted patients of decompensated chronic liver diseases. **Result:** Clinical improvement was noted in all three modes of treatment but there is no statistically significant difference in clinical improvement of hepatic encephalopathy when compared amongst each of three modes of treatment. There was obvious reduction of short term mortality or clinical down gradation of hepatic encephalopathy grade after 7 days treatment using lactulose or rifaximin or combined lactulose and rifaximin but there was no statistically significant difference in this regard among these three modes of treatment. **Conclusion:** All three modes of treatment are equally effective though combination therapy is little better.

**Key words:** Decompensated Chronic Liver Diseases; Hepatic Encephalopathy; Rifaximin; Lactulose; Mortality

## INTRODUCTION

Hepatic encephalopathy (HE) is a potentially reversible neuro-psychiatric and functional syndrome occurring in 50% - 70% of patients with advanced liver disease and or portosystemic shunting.<sup>1</sup> It occurs in presence of insufficient hepatic clearance of toxic products absorbed from the intestine resulting in neuro-chemical abnormalities after crossing the blood brain barrier.<sup>2</sup> The toxic products possibly implicated in the aetiology of hepatic

encephalopathy are ammonia, false neuro-transmitters (octopamine, phenyl-ethanolamine), gamma-amino butyric acid, short chain fatty acids, mercaptans, neuro-steroids and manganese.<sup>3</sup>

The clinical manifestations of hepatic encephalopathy range from altered mental status to deep coma.<sup>4</sup> Clinical diagnosis is not are considered the gold standard for diagnosis. The clinical diagnosis of overt hepatic encephalopathy is based on two concurrent types of

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### Address for Correspondence:

Dr. Uttam Biswas, 1680 Madurdaha, EKTP phase -4, Kolkata -700107. **Mobile No:** +91-9832018092. **E-mail:** druttambiswas@gmail.com

symptoms, impaired mental status, as defined by the Conn score (also called West Haven criteria) on a scale from 0-4, with higher score indicating more severe impairment,<sup>5</sup> and impaired neuro-motor function.<sup>6</sup> Conn score (West Haven score) is recommended by the working party on hepatic encephalopathy<sup>7</sup> for assessment of overt hepatic encephalopathy in clinical trials.

Most of the hepatic encephalopathy patients recover without permanent neurological impairment. Patients with chronic hepatic encephalopathy have either episodic or persistent symptoms. Patients with recurrent episodes, hepatic encephalopathy may be triggered by non-compliance to therapy or precipitated by infection, gastrointestinal bleeding, constipation, high protein diet, dyselectrolytaemia. In between episodes of hepatic encephalopathy, the mental status of the patient may be normal. Persistent hepatic encephalopathy may not be reversed despite medical treatment. These patients may have increased muscle tone, ataxia, dysarthria, apraxia, dementia, parkinsonism (without resting tremor), myelopathy (spastic paraparesis, hyperreflexia, extensor plantar response).

Lactulose, non-absorbable disaccharide reduces the absorption of ammonia through cathartic effect and by altering colonic pH. Lactulose is currently recommended as the first-line pharmacological treatment for hepatic encephalopathy by the practice guideline proposed by American College of Gastroenterology.<sup>8</sup> Treatment of hepatic encephalopathy is multifactorial and includes the management of precipitating factors and is to use lactulose, which results in colonic acidification, subsequently decreases the gut ammonia absorption into porto-systemic circulation and thereby decreases the availability of blood ammonia to cross the blood brain barrier. Rifaximin is a semi-synthetic, gut selective, minimally absorbed broad spectrum oral anti- microbial agent which has in vitro activity against gram-positive, gram-negative, aerobic and anaerobic enteric bacteria with less side effect and low risk of resistance.<sup>9,10</sup> The efficacy of rifaximin, a minimally absorbed oral antibiotic, is well documented in the treatment of acute hepatic encephalopathy. Rifaximin received approval from the US Food and Drug Administration in March 2010 for the treatment of hepatic encephalopathy.

Our study is to review the comparison of the effectiveness of Rifaximin (1200mg/day, in 3 divided doses) alone or in combination with Lactulose (60gram/day, in divided doses) or Lactulose (60gram/day) alone to reduce the short term mortality and clinical improvement in hepatic encephalopathy of any grade of any cause in adult (>18 years) admitted with patients decompensated chronic liver diseases.

### Aims and objectives

The purpose of this study is to compare the effectiveness of three different modes of treatment for hepatic encephalopathy for 7 days, in terms of short term mortality and clinical improvement. These three modalities of treatment in hepatic encephalopathy are :

Group- A: Lactulose (60 gram /day) with Rifaximin (1200 mg/day)

Group- B: Lactulose (60 gram /day) alone

Group- C: Rifaximin (1200 mg/day) alone.

## MATERIALS AND METHODS

In this prospective randomized control trial, we have included 90 adult (>18 years) admitted patients of decompensated chronic liver diseases of any cause of any grade of HE irrespective of sex and religion. Patients were randomized to treat with either following agent/s for 7 days with the doses -a) Lactulose- 60 gram/day (20 gram thrice a day), b) Rifaximin - 1200 mg. /day (400 mg. thrice a day), c) Rifaximin -1200 mg/day (400 mg thrice a day) and Lactulose, 60gm/day (20 gm thrice a day).

### Inclusion criteria

Adult (>18years) admitted patients of both sexes with decompensated chronic liver disease of any cause of any grade of hepatic encephalopathy.

### Exclusion criteria

Hepatic encephalopathy patients complicated with haematemesis and or melena, hepato-renal syndrome, hepato -pulmonary syndrome, hepato-cellular carcinoma, spontaneous bacterial peritonitis, dyselectrolytaemia, other metabolic encephalopathies severe comorbidities such as congestive cardiac failure, pulmonary diseases, kidney diseases, neuro-psychiatric illness, sepsis, h/o allergy with rifaximin and or lactulose.

### Study technique

After obtaining approval from Institutional ethical committee, collection of data were taken from cases after taking consent from patients parties of hepatic encephalopathy of any grade of any cause admitted in medicine ward by the following process:

Clinical examination and mental function assay by clinical methods, standard questionnaire. Categorization of the patients into different grades of hepatic encephalopathy before randomisation according to West Haven criteria of altered mental status (also called Conn score). Randomization of the patients; treated the patients with rifaximin and lactulose or lactulose or rifaximin for 7days after treatment clinical and mental function examination and grading of hepatic encephalopathy. Short-term

mortality /clinical deterioration /clinical improvement were noted with the three modes of treatment.

### End point of study

After the completion of proposed therapy for 7 days, re-categorised the study patients as per West Haven score.

## RESULTS

In our study, ninety patients of decompensated chronic liver diseases were selected and randomized to treat with either lactulose or rifaximin or both lactulose and rifaximin for 7 days. The mean age of the patients was 48.47 years. The age group of 46-55 years was the most predominant followed by 36-45 years age group and both these age groups comprised of about 59% of sample size in this study. Male and female ratio of the sample was 6:1. Male subjects (85.56%) were more than females (14.44%) (Table-1).

In our study we have found that post-treatment clinical improvement occurred maximally in combined treatment group (93%), followed by rifaximin group (83%) and lactulose group (73%), but the differences of outcome among three groups are not statistically significant ( $p = 0.115$ ) (Table-2).

Most deaths occurred in lactulose (16.67%) group, followed by rifaximin (10%) group. Least deaths occurred in combined drug treatment group (3.33%). But this is not statistically significant ( $p = 0.227$ ) (Figure-1).

So it is observed that, there is no short term mortality difference in three modes of treatment in hepatic encephalopathy. Our study showed that clinical down gradation occurred more in lactulose group (10%), followed

by in rifaximin group (6.67%) and least in combine drug treatment group (3.33%). These apparent differences among the groups are not statistically significant ( $p = 0.585$ ) (Figure-2).

## DISCUSSION

Most common age group affected by hepatic encephalopathy in our study was 46-55 years (33.33%) followed by 36-45 years (25.56%). The mean age of the sample population was 48.47 years. Male suffered more than female from decompensated chronic liver diseases and male to female ratio was 6:1.

In our study, most short-term mortality and clinical down gradation after treatment occurred in lactulose (16.67% and 10%) group, followed by rifaximin (10% and 6.67%) group. Least deaths and clinical down gradation were observed in combined drug treatment group (3.33% and 3.33%). There was prominent treatment benefit to reduce the short-term mortality and clinical down gradation in each treatment group. But these differences in short term mortality and down gradation among different group of treatment are not statistically significant; there were no significant differences in reducing short term mortality ( $p=0.227$ ) or clinical down gradation ( $p=0.585$ ) among three different modes of treatment. It was also noted that post-treatment clinical improvements were occurred maximally in combined treatment group (93%), followed by rifaximin group (83%) and lactulose group (73%). Our study revealed that there was treatment benefit to increase the clinical improvement with each modes of treatment but the differences in clinical improvements among three groups were not statistically significant ( $p = 0.115$ ). So, from our study it was found that there was no true difference of treatment outcome among three treatment groups using lactulose or rifaximin or both of them.

A meta-analysis of randomized controlled trials comparing disaccharides versus antibiotics for the treatment of hepatic encephalopathy has shown superior outcomes with the use of antibiotic therapy<sup>11</sup> and sub-group analysis of five studies comparing rifaximin to disaccharides favored the use of rifaximin,  $p = 0.04$ .<sup>12</sup> A recent study conducted in Spain found that rifaximin (1200 mg/day) and lactulose (60g/day) administered for 5-7 days showed approximately,

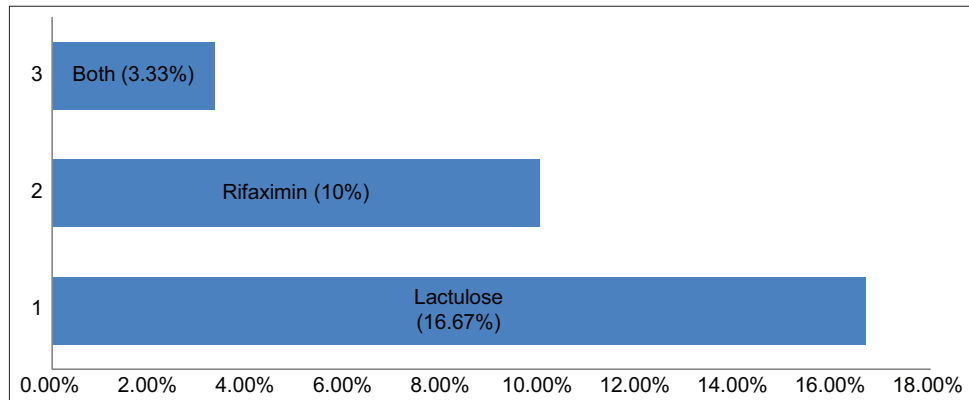
**Table 1: Age group distribution of sample population (N=90)**

Age in years	Number	Percentage
18-35	12	13.33
36-45	23	25.56
46-55	30	33.33
56-65	19	21.11
66-75	06	06.67
Total	90	100.00

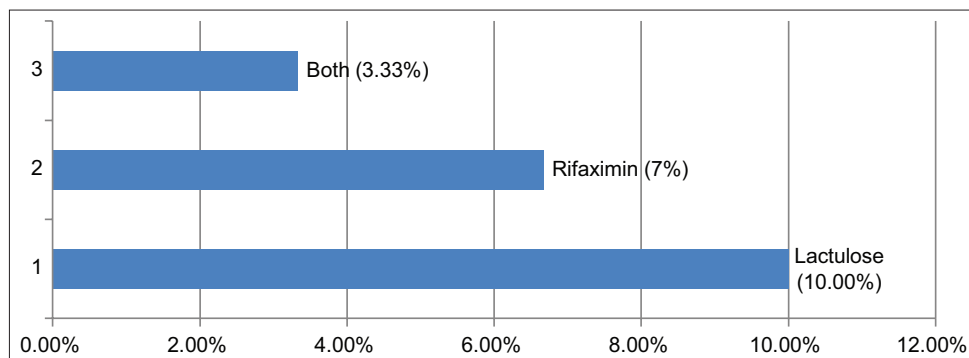
Male and female ratio of the sample was 6:1.

**Table 2: Comparison of clinical outcomes in three modes of treatment (N=90)**

Treatment group	Clinical improvement	Clinical deterioration	Total	P- Value
(1) Lactulose	22 (73%)	08 (27%)	30 (100%)	0.115
(2) Rifaximin	25 (83%)	05 (17%)	30 (100%)	
(3) Lactulose and rifaximin	28 (93%)	02 (07%)	30 (100%)	
Total	75 (83%)	15 (17%)	90 (100%)	



**Figure 1:** Comparison of deaths in three modes of treatment



**Figure 2:** Figure shows comparison of clinical down gradation of hepatic encephalopathy grade in three groups of treatment

80% symptomatic improvement in both groups of acute hepatic encephalopathy.<sup>13</sup>

Some studies have been conducted to support the use of rifaximin instead of or in addition to lactulose/ lactitol in the treatment of acute hepatic encephalopathy.<sup>13,14</sup> Yong-Han Paik, et. al confirmed that rifaximin is as effective as lactulose for the treatment of hepatic encephalopathy in Korean patients.<sup>15</sup>

## CONCLUSION

Clinical improvement was noted in all three modes of treatment but there was no statistically significant difference among each of three modes of treatment and there was obvious reduction of short term mortality or clinical down gradation of hepatic encephalopathy grade after 7 days treatment using lactulose or rifaximin or both but there was no statistically significant difference in this regard among these three modes of treatment.

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#### Author's Contributions

**SKP** - Concept and design of the study; prepared first draft of manuscript; **UB** - Interpreted the results; reviewed the literature and manuscript preparation; **PRC** - Statistically analysed and interpreted, preparation of manuscript and revision of the manuscript; **DRC** - Statistically analysed and interpreted, preparation of manuscript and revision of the manuscript; **AD** - Statistically analysed and interpreted, preparation of manuscript and revision of the manuscript; **AR** - Concept, coordination, review of literature and manuscript preparation.

#### Work attributed to:

R.G.Kar Medical College and Hospital, Kolkata, India.

#### Orcid ID:

Dr. Uttam Biswas - <https://orcid.org/0000-0002-4497-4478>  
Dr. Shyamal Kanti Pal - <https://orcid.org/0000-0001-8504-4050>  
Dr. Pallabi Ray Chaudhuri - <https://orcid.org/0000-0002-5859-373X>  
Dr. Debanjan Roychowdhury - <https://orcid.org/0000-0002-7379-9824>  
Dr. Abhranil Dhar - <https://orcid.org/0000-0003-4282-9581>  
Dr. Anirudhda Roy - <https://orcid.org/0000-0003-2119-0491>

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