A Randomized Controlled Trial Comparing the Efficacy of a Combination of Rifaximin and Lactulose with Lactulose only in the Treatment of Overt Hepatic Encephalopathy

Shakeb Hasan¹, Saikat Datta²*, Sharmistha Bhattacherjee³, Smarajit Banik⁴, Sandip Saha⁴, Dipanjan Bandyopadhyay⁵

Abstract

**Background:** Hepatic encephalopathy (HE), or portosystemic encephalopathy, represents a reversible decrease in neurologic function caused by liver disease, and treatment has traditionally been with non-absorbable disaccharides along with antibiotics and supportive measures. The present study was undertaken to evaluate if their combination therapy were superior to the established therapy in management of HE.

**Methods:** Ninety six (96) patients of hepatic encephalopathy were randomly assigned to receive either lactulose and rifaximin in standard dosage or lactulose only and their response to therapy was monitored using standard assessment tools. The statistical analysis was done using Kaplan–Meier methods to estimate the percentage of patients maintaining survival over time.

**Results:** The patients who were on lactulose and placebo revealed to have lower mortality than those on lactulose and rifaximin. Also, improvement in neurological status was of Grade 1 or more was more in patients on lactulose and placebo when compared to those on lactulose and rifaximin. Although survival analysis revealed no statistical difference between two groups, the mean survival in the placebo group was higher.

**Conclusion:** The present study reveals that improvement in neurological status of the group treated with lactulose only was that of a higher percentage than that of the group being treated with lactulose and rifaximin, which reiterates the recommendation that lactulose be used as a first line therapy in overt hepatic encephalopathy (OHE). Also the outcome was better in patients who had a lower grade of encephalopathy on admission.

Introduction

Hepatic encephalopathy is a neuropsychiatric syndrome caused by hepatic insufficiency associated with acute or chronic liver disease. The cause is considered to be the body’s inability to remove ammonia from the blood stream, and the resultant accumulation of neurotoxins in the blood affecting brain function. It has been reported that approximately 70% of cirrhotic patients present with subclinical or mild hepatic encephalopathy and 23-40% progress to a more severe form of the disease. One and three year survival rates after experiencing an episode of hepatic encephalopathy have been reported to be 42% and 23% respectively.¹

The diagnosis of overt hepatic encephalopathy (OHE) is basically a clinical diagnosis utilising clinical scales to analyse its severity. Specific quantitative tests are only needed in study settings. The gold standard is the West Haven criteria (Conn score).²

Editorial Viewpoint

- Traditionally hepatic encephalopathy is treated with non-absorbable disaccharides along with antibiotics and supportive measures.
- This study reiterates role of lactulose as first-line therapy in hepatic encephalopathy.
Treatment of HE has evolved slowly over the last 50 years, with several breakthroughs.\(^8\) Options include Lactulose (\(\beta\)-galactosidofructose) and lactitol (\(\beta\)-galactosidosorbitol) as initial treatment. Once in the colon, lactulose is fermented by anaerobic bacteria yielding important weak acids and gases which leads to the acidification of ammonia into ammonium resulting in its poor absorption. Additionally, antibiotics are used to eliminate the ammonia producing gut bacteria, thus reducing the total ammonia load. Neomycin was one of the first antibiotics used in HE. Subsequently, various other antibiotics have been tried with varied results.

Rifaximin is a minimally absorbed oral antimicrobial agent that is concentrated in the gastrointestinal tract, 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.\(^8\) Rifaximin has been used for the therapy of HE in a number of trials comparing it with placebo, other antibiotics, nonabsorbable disaccharides, and in dose-ranging studies. These trials have revealed that the effect of rifaximin was equivalent or superior to the compared agents with good tolerability.\(^10\)

Rifaximin has been found to significantly reduce the risk of an episode of hepatic encephalopathy, in comparison to placebo, over a 6-month period. A breakthrough episode of hepatic encephalopathy occurred in 22.1% of patients in the rifaximin group, as compared with 45.9% of patients in the placebo group.\(^11\)

In a systematic review, rifaximin has been found to be at least equally effective or superior to non-absorbable disaccharides and antimicrobials in relieving signs or symptoms observed in patients with mild-to–moderately severe HE.\(^12\) In another meta-analysis, no serious adverse events were reported following either rifaximin or disaccharides therapy.\(^13\)

In this context, the current study was undertaken to compare a combination therapy against monotherapy with the hypothesis that response of treatment with lactulose and rifaximin is non-inferior when compared to standard therapy with lactulose only.

### Methodology

#### Study design

A non-inferiority type of randomized controlled trial was conducted among the indoor patients of the General Medicine ward of North Bengal Medical College and Hospital.

#### Study population

Adult patients with diagnosed chronic liver disease having encephalopathy (grade I to IV), after exclusion of metabolic/infective causes, were included in the study.

#### Exclusion criteria

- Age <18yrs
- Presence of any diagnosed neuropsychiatric illness and/or current use of antipsychotic/antidepressant medications
- Presence of any intestinal obstruction or inflammatory bowel disease
- Diagnosed hypersensitivity to Rifamycin or disaccharides
- Serum creatinine > 1.5 mg/dl
- Electrolyte abnormality (sodium <125 or >150 mEq/l)
- Minimal hepatic encephalopathy [Conn grade 0]\(^2\)
- Hypoglycaemia (capillary blood glucose < 70 mg/dl)
- Consent not given

A caregiver was present with the patient at all times to monitor any changes in the patient’s health or HE status and to ensure that the patient takes the study medications as scheduled.

#### Sampling

According to previous studies, anticipated percentage of study...
The test was run to determine if there were differences in the survival distribution for the two groups.

Results and Analysis

Of a total of 120 patients screened for the study, 96 were enrolled. Finally, a total of 91 patients were randomised to receive rifaximin (n = 45) or placebo (n = 46) in the trial.

The mean age of the study population was 44.97 ± 10.448 years. 87.3% population was male in the present study. The majority of the study population was from the rural areas (63.3%). 91.1% of the study population had history of regular alcohol intake. 53.2% of the study population had history of constipation on admission.

11 patients (13.9%) of the population had a history of upper GI bleed in the form of haematemesis. 24.1% of the population under study had a history of melaena. The differences were statistically not significant.

89.9% of the total population had ascites at the time of admission. The demographical and baseline disease characteristics were similar in both the groups (Table 1).

The overall mortality was 25.4%. The rifaximin group had a mortality

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**Table 1: Sociodemographic characteristics and presenting features of patients in two groups. (N=91)**

<table>
<thead>
<tr>
<th></th>
<th>Rifaximin group</th>
<th>Placebo group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean ± SD)</td>
<td>44.73 ± 10.59</td>
<td>44.98 ± 10.12</td>
<td>0.910</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>36 (80.0%)</td>
<td>38 (82.6%)</td>
<td>0.793</td>
</tr>
<tr>
<td>Female</td>
<td>9 (20.0%)</td>
<td>8 (17.4%)</td>
<td></td>
</tr>
<tr>
<td>Alcohol addiction</td>
<td>42 (93.3%)</td>
<td>39 (84.8%)</td>
<td>0.315</td>
</tr>
<tr>
<td>Presenting signs and symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>22 (48.9%)</td>
<td>28 (60.9%)</td>
<td>0.174</td>
</tr>
<tr>
<td>Haematemesis</td>
<td>9 (20.0%)</td>
<td>5 (10.9%)</td>
<td>0.180</td>
</tr>
<tr>
<td>Melaena</td>
<td>12 (26.7%)</td>
<td>11 (23.9%)</td>
<td>0.813</td>
</tr>
<tr>
<td>Jaundice</td>
<td>34 (75.6%)</td>
<td>36 (78.3%)</td>
<td>0.807</td>
</tr>
<tr>
<td>Ascites</td>
<td>43 (95.6%)</td>
<td>42 (91.3%)</td>
<td>0.677</td>
</tr>
<tr>
<td>Initial Sensorium level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0 (0.0%)</td>
<td>2 (4.3%)</td>
<td>0.477</td>
</tr>
<tr>
<td>2</td>
<td>13 (28.9%)</td>
<td>10 (21.7%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>17 (37.8%)</td>
<td>19 (41.3%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>15 (33.3%)</td>
<td>15 (32.6%)</td>
<td></td>
</tr>
<tr>
<td>SBP (Mean ± SD)</td>
<td>117.38 ± 22.02</td>
<td>115.87 ± 18.06</td>
<td>0.677</td>
</tr>
<tr>
<td>DBP (Mean ± SD)</td>
<td>71.96 ± 13.54</td>
<td>72.02 ± 12.47</td>
<td>0.981</td>
</tr>
</tbody>
</table>

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**Table 2: Outcome in both the groups (n=91)**

<table>
<thead>
<tr>
<th></th>
<th>Rifaximin Group</th>
<th>Placebo Group</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unchanged/worsened</td>
<td>12 (27.9%)</td>
<td>8 (20.0%)</td>
<td>0.646</td>
</tr>
<tr>
<td>Improved</td>
<td>31 (72.1%)</td>
<td>32 (80.0%)</td>
<td>1.794</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>32 (74.4%)</td>
<td>32 (80.0%)</td>
<td>0.727</td>
</tr>
<tr>
<td>Present</td>
<td>11 (25.6%)</td>
<td>8 (20.0%)</td>
<td>2.046</td>
</tr>
</tbody>
</table>

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Summary

population in the Rifaximin and Lactulose combination group that responds to treatment would be 76% and in Lactulose group 50%. Assuming dropout rate to be 10%, 95% confidence interval and 80% power, the sample size was calculated as 46 each in test group and in control group. Randomization to each treatment arm was in a 1:1 allocation ratio. Block randomization using variable block sizes was used.

Data collection

A chronological log of all enrolled patients was maintained. Each enrolled patient was assigned the next available sequential study code. The assigned number corresponded to a coded, sealed, packet containing bottle of 30 tablets of either Rifaximin or placebo.

After enrolling, the patients were randomly divided into two groups—one receiving Lactulose 15ml three to four times a day titrated so as to produce 3-4 loose stools per day along with Rifaximin 400 mg thrice daily, and the other group receiving Placebo with Lactulose. Both groups received supportive measures as indicated (including but not limited to IV antibiotics, enema, inotropic support, blood and blood products) (Figure 1).

Follow up

The patients were followed up till recovery of Hepatic Encephalopathy or a maximum of ten days.

Endpoint of the study

Any reduction in grade of encephalopathy according to Conn scale was considered as improved, and any increase in encephalopathy grade was considered as worsened.

Statistical analysis

Data were entered in Microsoft Excel datasheet and demographical and baseline disease characteristics were summarised using descriptive statistics. Kaplan–Meier methods were used to estimate the percentage of patients maintaining survival over time. A log rank test was run to determine if there were differences in the survival distribution for the two groups.

Results and Analysis

Of a total of 120 patients screened for the study, 96 were enrolled. Finally, a total of 91 patients were randomised to receive rifaximin (n = 45) or placebo (n = 46) in the trial.

The mean age of the study population was 44.97 ± 10.448 years. 87.3% population was male in the present study. The majority of the study population was from the rural areas (63.3%). 91.1% of the study population had history of regular alcohol intake. 53.2% of the study population had history of constipation on admission.

11 patients (13.9%) of the population had a history of upper GI bleed in the form of haematemesis. 24.1% of the population under study had a history of melaena. The differences were statistically not significant.

89.9% of the total population had ascites at the time of admission. The demographical and baseline disease characteristics were similar in both the groups (Table 1).

The overall mortality was 25.4%. The rifaximin group had a mortality
of 28.9% as compared to 21.2% in the placebo group. 70.3% of the total population had improvement in the neurological status. 68.4% of the patients in the rifaximin and lactulose whereas 72.2% of patients on lactulose and placebo showed improved neurological status by 1 or more grade (Table 2).

100% of the cases having initial sensorium level of Grade 1 improved, 89.5% presenting with Grade 2, 65.5% with initial Grade 3 and 58.3% with Grade 4 improved post admission.

Survival analysis by Kaplan Meier method revealed no difference in the overall survival distributions between the groups. The mean survival in the placebo group was higher (Figure 2).

Discussion

The study populations in the two groups were similar with respect to age. 38% of the study population was in the age group 40-49 years, 27.9% in 50-59 year age group and 16.5% in the age group of 30-39 years. Patil et al reports that age wise, prevalence of liver cirrhosis is higher in age group of 31-40 years i.e. 30 cases (30%) and next highest in age group of 31-40 years i.e. 28 cases (28%).

63% of the total study population were from rural area. It has been reported that prevalence rate is high in the illiterate patients as compared to literate patients. In rural and urban area wise, higher number of cases have been seen in rural area patients i.e., 62% as compared to urban area patients i.e. 38%.

Incidence of HE in the present study was higher in males (87.3 % of the total study population). The sex wise distribution of prevalence of liver cirrhosis cases has been reported to be higher in males (74%), as compared to females, in whom the prevalence rate was 26%.

91% of the population in the present study was alcoholic.

Sundaram et al have also found that the leading cause of cirrhosis in India is alcohol consumption. 14% and 24 % population in this study had history of hematemesis and melaena, respectively. It has been reported that 30 to 40% of patients with compensated cirrhosis of the liver and 60% of patients with ascites present with esophageal varices and associated increased chance of upper GI bleed.

92.4% of the patients had history of abdominal swelling, and 89.9% were having ascites on admission. This can be correlated with a study where overt hepatic encephalopathy has been reported in subjects without cirrhosis with extensive porto systemic shunting.

The rifaximin group had a mortality of 28.9% as compared to the placebo group where the mortality was found to be 21.2%. This is in contrast to the study by Sharma et al where a mortality of 23.8% in rifaximin and lactulose group against 49.1% mortality in lactulose and placebo group was reported, with a p value of < 0.05.

According to Bustamante et al it was 42% at 1 year of follow up and 23% at 3 years. Mortality of 15% has been reported in developed countries of the world.

68.4% of the patients in the rifaximin and lactulose group of this study had improvement in neurological status whereas 72.2% of patients on lactulose and placebo showed improved neurological status by 1 or more grades, as assessed by Conn score (West Haven criteria).

Sharma et al reported the respective improvement to be 76% and 50.8%. Mas et al had reported equal effectiveness of rifaximin and lactitol, however most of the patients were in grade 1 or 2 HE.

Conclusion

The present study reveals that improvement in neurological status of the group treated with lactulose was that of a higher percentage than that of the group being treated with lactulose and rifaximin.

Although the p value is > 0.05, however the study reiterates the recent recommendation that lactulose be used as the first line therapy in OHE.

Also the outcome was better in patients who had a lower grade of encephalopathy on admission.

Mortality rate is still an important concern, with this study projecting an overall mortality of 25.4% of which 61% were in the group receiving combination therapy.

The statistically higher mortality rate and the worsening of neurological status could be attributed to a small sample size, a co-existing sepsis or a worse grade of encephalopathy on presentation, or even to a preceding history of HE in the past, all of which do worsen the prognosis as has been seen on reviewing the available literature.

Limitations

1. Monitoring of all patients in closed environment, i.e. intensive care facility, might have affected some outcomes

2. Etiological investigation would be another avenue to pursue for relative prognosis and expected response

References


