Original article

Comparison of the Effectiveness of Rifaximin plus Lactulose versus Lactulose Alone in Overt Hepatic Encephalopathy in Terms of Complete Reversal

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ABSTRACT

Background: Hepatic encephalopathy is a serious complication of liver disease, marked by cognitive impairment and potentially life-threatening consequences. Lactulose has long been a standard treatment, but its effectiveness may be limited. Adding rifaximin to lactulose has shown promising results in managing overt hepatic encephalopathy (OHE). This study compared the frequency of complete reversal of encephalopathy by rifaximin plus lactulose versus lactulose alone in patients with OHE.

Patients and methods: A randomized controlled trial was carried out at the Department of Gastroenterology, DHQ Teaching Hospital Gujranwala. The patients diagnosed with hepatic encephalopathy (age range = 18-60 years) were included. On the contrary, patients with serum creatinine of >1.5 mg/dl at admission, diagnosed with hepatocellular carcinoma, active alcohol intake (<4 weeks) and patients with significant comorbidities like CVA, epilepsy, and dementia were excluded from the study were not included in the study. A total of 90 patients were randomized into two equal groups; Group A and Group B. Group A patients received a combination therapy of Rifaximin (550mg tablet twice daily) and lactulose (30-60 ml thrice a day). Group B patients received lactulose (30-60 ml thrice times daily) and a placebo capsule (sugar) thrice daily. Both groups were monitored for achievement of optimal bowel function (two to three semisoft stools per day).

Results: The mean age of patients was 44.9 years. Overall there were 66 (73.3%) males and 24 (26.7%) females. The mean MELD scores in group A and group B were 33.76 ± 16.76 and 34.36 ± 15.85, respectively. The mean duration of liver cirrhosis in group A and group B was 6.49 ± 2.25 and 6.67 ± 2.40, respectively. In group A, a complete reversal of HE was seen in 38 (84.4%) cases while in group B the complete reversal of HE was observed in 24 (53.3%) cases (p-value <0.05). When data was stratified for age, gender, baseline Child-Turcotte- Pugh class, MEL score, grades of HE and duration of disease the frequency of complete reversal of HE was significantly high (p-value < 0.05) in group A as compared to group B in all the subgroups.

Conclusion: The combination of Rifaximin with lactulose is more effective in treating overt hepatic encephalopathy compared to lactulose alone in terms of complete reversal.

Keywords:

Overt Hepatic Encephalopathy, Rifaximin, Lactulose, Reversal of OHE, Model for End-Stage Liver Disease (MELD)

INTRODUCTION

Liver cirrhosis ranks as the fourteenth leading cause of mortality worldwide, contributing to between 1% to 57% of deaths depending on disease severity.[1] Despite advancements in healthcare, the morbidity and mortality associated with liver cirrhosis are on the rise, even in developed nations.[1] Progression to advanced stages of the disease can lead to potentially fatal complications.[2]

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, along with alcohol consumption, are recognized as the primary global etiologies of liver cirrhosis.[2,3] Hepatic encephalopathy (HE) refers to a spectrum of neurological changes occurring during acute liver failure or chronic liver injury.[4,5] Up to half of all patients with cirrhosis will develop HE, particularly in the decompensated stage.[6] While several key pathogenic factors have been identified, including elevated brain ammonia levels, neurosteroid imbalances, and neuroinflammation, the understanding of the precise mechanisms remains incomplete.[5]

HE is classified into two main categories including overt hepatic encephalopathy (OHE) and covert hepatic encephalopathy (CHE).[4] Management strategies

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involve two phases including induction and maintenance of remission. In most cases of significant OHE, precipitating factors such as infection, gastrointestinal bleeding, or medications need to be identified and managed.[5] Initial treatment typically involves nonabsorbable disaccharides like lactulose, with additional options including antibiotics (like rifaximin) and probiotics.[4] Other interventional therapies include glycerol phenylbutyrate, ornithine phenylacetate, L-ornithine-L-aspartate and albumin infusion.[5,6]

Rifaximin, an oral gut-selective antimicrobial agent, has demonstrated efficacy in reducing the recurrence of OHE and related hospitalizations.[7] A study reported a significant improvement with complete reversal of HE when rifaximin was added to lactulose treatment compared to lactulose alone (76% *vs.* 50.8%, respectively ($p<0.004$).[8]

Given limited local data, there was a need to investigate the effectiveness of rifaximin in combination with lactulose versus lactulose alone for treating OHE in local population. Prior research has suggested that the combination therapy may offer advantages, potentially leading to higher rates of OHE reversal and reduced mortality by preventing related complications. This study aimed to assess the role of added rifaximin in the outcome of management of OHE.

PATIENTS AND METHODS

The study was approved by ethical review committee. A sample size of 90 cases was calculated with 95% confidence level, 80% power of study, and 5% level of significance, for expected frequencies of complete OHE reversal at 76% in the lactulose plus rifaximin group and 50.8% in the lactulose-only group.[8] Inclusion criteria comprised patients aged 18-60 of both genders diagnosed with cirrhosis and hepatic encephalopathy, excluding those with serum creatinine levels >1.5mg/dl at admission, recent alcohol intake within 4 weeks, known hepatocellular carcinoma, or significant comorbidities such as cerebrovascular accidents (CVA), epilepsy, or dementia. Baseline information including age, gender, contact details, and a comprehensive set of laboratory assessments (serum electrolytes, arterial ammonia, liver and kidney function tests, complete blood count, blood sugar, prothrombin time, INR and viral markers) along with abdominal ultrasound with Doppler imaging were collected for all participants. Participants were randomized to Group A and Group B. Group A received rifaximin (550 mg tablet twice daily) in combination with lactulose (30-60 ml three times daily) to achieve optimal bowel function (two to three semisoft stools per day). Group B received lactulose alone (30-60 ml three times daily) and a placebo capsule (sugar) three times daily to match the dosing schedule of Group A. Treatment administration for both groups was conducted via nasogastric tube under stringent intensive care monitoring, continuing until complete resolution of hepatic encephalopathy (HE) or up to a maximum of 10 days. Once HE was cured, patients in both groups continued on their respective medications. Complete reversal of HE, assessed after 7 days using the West Haven criteria. Data was entered in SPSS version 22 statistical analysis. Quantitative variables such as age, MELD score, and duration of liver cirrhosis were presented as Mean ± S.D. Qualitative data including gender, Child-Turcotte-Pugh class, grades of HE, and complete reversal of HE was summarized using frequencies and percentages. The Chi-square test was employed to compare the complete reversal of HE between study groups, with a significance level set at $p\leq0.05$. Data was stratified by age, gender, baseline Child-Turcotte-Pugh class, MELD score, grades of HE, and duration of disease to assess potential effect modifiers. Post-stratified Chi-square tests were conducted with a significance level of $p\leq0.05$.

RESULTS

The mean age of the patients was 44.92 ± 11.3 years. Most participants were aged 40-60 years (72.1%) and were males (73.3%). Mean MELD score was 34.06 ± 16.22, with 55.5% patient's having a score of ≥30. The duration of liver cirrhosis was 6.58 ± 2.32 years, with 56.7% having cirrhosis for ≥6 months. Child-Pugh Class distribution was primarily Class B (57.8%), followed by Class C (42.2%). The majority of participants had severe HE (Grade 4, 71.1%). Both the groups were statistically comparable (p-value>0.05) as given in Table 1.

Results showed significantly higher rates of complete reversal in Group A (84.4%) compared to Group B (53.3%) with a total of 68.9% achieving reversal in Group A versus 31.1% in Group B ($p=0.001$). These findings indicate the efficacy of the treatment in achieving complete reversal of HE, as given in Table 2. Stratification of complete reversal of HE on the basis of age, gender, MELD score, Child Pugh Class, HE grade and duration of liver cirrhosis produced similar significant results for all the sub groups (p-value <0.05), as given in Table 2.

Table 1: Characteristics of the participants

Characteristics	Total N=90	Group A N=45	Group A N=45
Age (mean±SD)	44.92±11.36	44.33±12.17	45.51±10.58
18-39 years	23 (25.5%)	12 (26.7%)	11 (24.4%)
40-60 years	67 (72.1%)	33 (73.3%)	34 (75.5%)
Gender			
Male	66 (73.3%)	31 (68.9%)	35 (77.8%)
Female	24 (26.7%)	14 (31.1%)	10 (22.2%)
MELD Score	34.06±16.22	33.76±16.76	34.36±15.85
<30	40 (44.4%)	25 (55.6%)	25 (55.6%)
≥30	50 (55.5%)	20 (44.4%)	20 (44.4%)
Duration of liver cirrhosis	6.58±2.32	6.49±2.25	6.67±2.40
< 6 Months	39 (43.3%)	26 (57.8%)	30 (66.7%)
≥ 6 Months	51 (56.7%)	19 (42.2%)	15 (33.3%)
Child-Pugh Class			
Class B	52 (57.8%)	23 (51.1%)	29 (64.4%)
Class C	38 (42.2%)	22 (48.9%)	16 (35.6%)
Grades of HE			
Grade 2	12 (13.3%)	6 (20.0%)	6 (13.3%)
Grade 3	14 (15.6%)	12 (15.6%)	2 (4.5%)
Grade 4	64 (71.1%)	27 (60.0%)	37 (82.2%)

Comparison of Group A and B showed insignificant difference between them for baseline characteristics with p-value >0.05.

Table 2: Comparison of complete reversal of HE between the study groups

Characteristics	Study group		p-value
	Group A	Group B	
Complete reversal	38 (84.4%)	24 (53.3%)	0.001
Age			
18-39 years	12 (100.0%)	6 (54.5%)	0.008
40-60 years	26 (78.8%)	18 (52.9%)	0.026
Gender			
Male	26 (83.9%)	20 (57.1%)	0.018
Female	12 (85.7%)	4 (40.0%)	0.019
MELD score			
<30	16 (80.0%)	10 (50.0%)	0.047
≥30	22 (88.0%)	14 (56.0%)	0.012
Child Pugh class			
Class B	18 (81.1%)	8 (50.0%)	0.037
Class C	20 (87.0%)	16 (55.2%)	0.014
HE Grade			
Grade 2	5 (83.3%)	4 (66.6%)	0.044
Grade 3	10 (83.3%)	1 (50.0%)	0.035
Grade 4	23 (85.2%)	32 (71.11%)	0.019
Duration of liver cirrhosis			
<6 months	21 (87.5%)	9 (60.0%)	0.047
≥6 months	17 (87.0%)	15 (50.0%)	0.024

Chi square test taking p-value ≤0.05 as significant.

DISCUSSION

Hepatic encephalopathy, a serious complication of liver disease characterized by cognitive impairment and significant morbidity, presents challenges in clinical management.[9] While lactulose has been a standard primary treatment, its efficacy can be suboptimal.[10] The addition of rifaximin to lactulose has shown promise in managing this condition, yet literature on this combination remains limited.[11,12]

In the present study, mean age of all patients was 44.92 ± 11.36 years, with an overall composition of 66 (73.3%) males and 24 (26.7%) females. Within Group A, there were 31 (68.89%) males and 14 (31.14%) females, and within Group B, there were 35 (77.78%) males and 10 (22.22%) females. This distribution closely mirrored that of the previously cited study.[12] In the current study, complete reversal of hepatic encephalopathy (HE) was achieved in 38 (84.4%) cases within Group A and 24 (53.3%) cases within Group B (p-value < 0.05).

Comparing findings of this study with previous local study[13] groups demonstrated comparable baseline characteristics, including mean age (p-value = 0.63), gender distribution (p-value = 0.71), Child-Pugh class (p-value = 0.74), and grade of hepatic encephalopathy (p-value = 0.66). Lactulose alone (Group A) was effective in 53.3% (32 out of 60) of cases, whereas 83.3% (50 out of 60) achieved hepatic encephalopathy reversal in Group B (Lactulose plus Rifaximin), a statistically significant difference (p-value = 0.0004). Another study enrolled on 124 patients, with 62 patients in each group (A & B). The efficacy rates for treating hepatic encephalopathy were 72.6% (45 out of 62) in Group A (Rifaximin plus Lactulose) and 51.6% (32 out of 62) in Group B (Lactulose alone).[14]

Bajaj and coauthors in 2021 analyzed 139 patients in viral and alcohol etiology subgroups, demonstrating fewer HE episodes and hospitalizations in those receiving rifaximin + lactulose compared to lactulose alone.[15] Wang and associates in China reported that combination of rifaximin and lactulose has demonstrated beneficial effects in hepatic encephalopathy.[16] When compared to lactulose alone, the addition of rifaximin enhances clinical efficacy and reduces mortality rates. Nevertheless, the specific impact of this combination on different types of HE remains uncertain and requires further investigation. One study from India demonstrated superior efficacy of combining lactulose with rifaximin compared to lactulose alone in the treatment of overt hepatic encephalopathy (HE).[8] Their findings suggested that this combination therapy led to better outcomes in managing HE symptoms and achieving resolution.

CONCLUSION

Frequency of complete reversal of HE was statistically higher when Rifaximin is added to lactulose in management of cirrhotic encephalopathy, the combination demonstrated greater effectives in treating overt hepatic encephalopathy compared to lactulose alone in terms of complete reversal.

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