ORIGINAL ARTICLE

Is Lactulose Plus Rifaximin Better than Lactulose Alone in the Management of Hepatic Encephalopathy?

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Abstract

Objective: To compare the efficacy of lactulose plus rifaximin with efficacy of lactulose alone in the treatment of hepatic encephalopathy.

Study Design: A randomized controlled trial.

Place and Duration of Study: Department of Medicine, Jinnah Hospital, Lahore, from December 2014 to June 2015.

Methodology: All patients who presented with hepatic encephalopathy due to decompensated chronic liver disease were randomly divided into two groups of 65 patients each. One group was given 30 ml thrice daily lactulose alone and the other lactulose plus rifaximin 550 mg twice daily for 10 days. Informed consents were taken from the participants' attendants. Grades II-IV hepatic encephalopathy was noted according to West-Haven Classification. All subjects were followed until 10 days after admission.

Results: The mean age of patients was 56.06 ±11.2 years, among which 46.9% were females and 53.1% were males. After ten days of follow-up, reversal was seen in 58.46% in lactulose alone group and 67.69% in lactulose plus rifaximin group (Chi-square p=0.276).

Conclusion: There was no difference in effectiveness of lactulose plus rifaximin and lactulose alone in treatment of hepatic encephalopathy.

Key Words: *Chronic liver disease. Hepatic encephalopathy. Lactulose. Rifaximin.*

INTRODUCTION

Hepatic encephalopathy is a serious life-threatening condition, ranging from mild motor and cognitive dysfunction to coma, and is potentially reversible if adequately treated.[1] The incidence of hepatic encephalopathy is higher in patients suffering from both liver cirrhosis and acute liver failure.[2] Bacteria residing in the intestine produce ammonia, which plays a role in the pathogenesis of hepatic encephalopathy.[3] Hepatic encephalopathy can be treated by reducing the production and absorption of this gut derived ammonia. Non-absorbable disaccharides are currently the main stay of the therapy.[4] A survival rate of 42% was reported by Bustamante *et al*. in patients with cirrhosis with first episode of hepatic encephalopathy at follow-up after a year and 23% at 3 years.[5]

Lactulose is a non-absorbable disaccharide. Systemic review of literature emphasized that effectiveness of lactulose was more than placebo to improve hepatic encephalopathy on short-term basis; however, there was no effect on mortality in the long run.[6] Diarrhea and abdominal pain may complicate treatment with lactulose.[7] Rifaximin is a semi-synthetic derivative of rifamycin and is virtually unabsorbed after oral administration.[8] It exhibits broad-spectrum antimicrobial activity against both aerobic and anaerobic gram-positive and gram-negative bacteria within the gastrointestinal tract.[9,10] In patients with liver dysfunction or renal insufficiency, adjustment of dosage is not required.[11,12] The therapeutic responses to anti-viral therapies can be affected by ethnicity, which is also reported to affect long-term prognosis of patients with advanced liver disease.[13,14]

A number of studies regarding efficacy of lactulose and rifaximin in patients of hepatic encephalopathy have been carried out, but with conflicting results. Decompensated liver cirrhosis, leading to hepatic encephalopathy, represents a major chunk of disease burden in Pakistan, leading to in-hospital stay and financial strain. No study has been published yet regarding Pakistani population.

The objective of this study was to compare the efficacy of lactulose plus rifaximin with lactulose alone in hepatic encephalopathy patients due to decompensated liver cirrhosis (CLD) in addition to usual treatment.

METHODOLOGY

This study was a randomized controlled trial conducted in the Department of Medicine, Jinnah Hospital, Lahore, from December 2014 to June 2015. All patients who presented with hepatic encephalopathy due to

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decompensated chronic liver disease (characterized by presence of coarse echotexture of liver on abdominal ultrasound) were included in the study. Patients having hepatic encephalopathy due to causes other than chronic liver disease, and patients allergic to the administered agents were excluded from the study.

Data was collected after approval from Medical Ethics Committee of AIMC/JHL. Selection of sample was from patients admitted in Medical Department, Jinnah Hospital Lahore. Informed consents were taken from the participants' attendants. Grades II-IV hepatic encephalopathy was noted according to West-Haven Classification. Demographic information, e.g. age, gender, address etc. were obtained. Single-blind was applied to reduce bias. The participants were divided into two groups, by lottery method. Group A was given lactulose 30 ml thrice daily. Group B was given lactulose 30 ml thrice daily plus rifaximin 550 mg twice daily.

All subjects were followed until 10 days after admission; final outcome (efficacy in terms of recovery from hepatic encephalopathy) was recorded in predesigned performa. The usual treatment was given to all patients as per hospital protocol.

Data was entered in SPSS version 20. Mean, standard deviation, and median (with IQR for not normally distributed variable) were calculated for quantitative variables (age of patients, duration of disease). Frequency and percentage was calculated for qualitative variables (gender of patients, socioeconomic status, grade of hepatic encephalopathy). Effect modifiers and confounders (age, gender, grade of hepatic encephalopathy, duration of disease) were controlled through stratification. Chi-square test was applied by taking p $\leq$0.05 to compare efficacy of lactulose plus rifaximin and lactulose alone.

RESULTS

A total of 130 patients fulfilling the inclusion criteria were enrolled in the study. The mean age of patients was 56.06 $\pm$11.2 years. The median age was 55.73 years with interquartile range value of 14. There were 46.9% females (61 patients) and 53.1% males (69 patients). Eighteen (13.8%) patients belonged to high socioeconomic status, 36.9% (48 patients) belonged to middle socioeconomic status; whereas, 49.2% (64 patients) belonged to low socioeconomic status.

At the start of the study out of 65 patients in group A, grade II encephalopathy was present in 26.15% (17 patients), grade III encephalopathy in 38.46% (25 patients) and grade IV encephalopathy in 35.38% (23 patients). After ten days of follow-up, reversal of hepatic encephalopathy was seen in 58.46% (38 patients) in group A.

In Group B, out of the 65 patients at the start of study, 40.0% (26 patients) had grade II encephalopathy, 36.92% (24 patients) had grade III encephalopathy and 23.07% (15 patients) had grade IV encephalopathy. After ten days of follow-up, reversal of hepatic encephalopathy was seen in 67.69% (44 patients) in group B (Table I).

Stratification for outcome was done with regard to age (p=0.256), gender (p=0.579), socioeconomic status (p=0.690), duration of disease (p=0.498), grade of encephalopathy at start of study (p <0.001, significant) and treatment given (p=0.276).

Table I: Stratification for outcome among patients with regard to grade of hepatic encephalopathy at the start of study (n=130).

Grade of hepatic encephalopathy at start	Outcome		Total
	No reversal	Reversal	
II	5 (3.84%)	38 (29.23%)	43
III	13 (10.0%)	36 (27.69%)	49
IV	30 (23.07%)	8 (6.15%)	38
Total	48	82	130

Pearson Chi-square value: 42.901, p-value < 0.001 (significant).

DISCUSSION

Hepatic encephalopathy is a serious life-threatening, but reversible condition which can be manifested in acute and chronic disease with ammonia being the major contributor.[1-3] As a result, the treatment of hepatic encephalopathy revolves around reducing production of ammonia and its absorption in the gut and also by improving the excretion of ammonia by modification of diet or drug therapy.[15]

At the moment, the most commonly used therapies for treating hepatic encephalopathy are lactulose and non-absorbable antibiotics. Sixteen lactulose, recommended as the first-line pharmacological treatment; however, is associated with abdominal cramps, severe diarrhea, nausea, flatulence, and dehydration.[17,7]

Antibiotics may be used as a therapeutic alternative to non-absorbable disaccharides for treating of hepatic encephalopathy.[18] Neomycin, non-absorbable aminoglycoside, prescribed for hepatic encephalopathy in the past, but its use is limited by ototoxicity and nephrotoxicity. Another antibiotics, metronidazole, which differs from neomycin in terms of bacterial spectrum, improves hepatic encephalopathy; however, the common use is limited by its potentially severe neurotoxicity in patients with cirrhosis.

Rifaximin, a semi-synthetic derivative of rifamycin having broad-spectrum antimicrobial activity, is not absorbed in the gut.[8] Its active form remains in high concentrations in gut and gets excreted in feces without causing significant systemic side effects such as nephrotoxicity.[9,10] Furthermore, previous studies have shown that it is effective at reducing hepatic encephalopathy in cirrhotics.

A randomized controlled trial conducted in India by Sharma *et al*. showed complete recovery from hepatic encephalopathy in 76% of patients treated with lactulose

plus rifaximin as compared to 50.8% of patients treated with lactulose alone.[12] The sample size was 120 patients, mean age of the patients was 39.4±9.6 years, while the male/female ratio was 89:31. A significant reduction in mortality was seen after treatment with lactulose plus rifaximin (23.8%) versus lactulose alone (49.1%). A meta-analysis was conducted in 2012 by Eltawil *et al*. in which 12 randomized controlled trials met the inclusion criteria, a total of 565 patients were a part of the study.[13] Clinical effectiveness of rifaximin was found to be equivalent to disaccharides or other oral antibiotics having odds ratio (OR) 0.96; 95% CI: 0.94-4.08 but with a better safety profile (OR 0.27; 95% CI: 0.12-0.59).[13] Another meta-analysis conducted in 2012 by Jiang *et al*. in which 5 trials met the inclusion criteria on a total of 264 patients demonstrated no significant difference between rifaximin plus lactulose and lactulose alone on improvement in patients of hepatic encephalopathy but rifaximin was better tolerated.[14]

The present study was a randomized study which was conducted to compare efficacy of lactulose plus rifaximin with that of lactulose alone for the treatment of hepatic encephalopathy. No relevant study and data were available on ethics background affect on the effectiveness of rifaximin for the treatment of hepatic encephalopathy.[15]

This study does not confirm that lactulose plus rifaximin is more effective in treatment of hepatic encephalopathy as compared to lactulose alone. Further, no significant difference between lactulose plus rifaxaimin and lactulose alone was found in terms of their efficacies. The authors believe more studies, involing a large sample size/number of patients, are required for identification of the factors determining responsiveness to rifaximin in hepatic encephalopathy.

All hepatic encephalopathy therapeutic trials can be criticized from the perspective of evidence-based medicine which includes definitions of study endpoints, control groups treatment, and the proper quantification of therapeutic effects.[1] Sanaka *et al*. described the difficulties of designing a good hepatic encephalopathy treatment trials.[16] The mental status evaluation system using the portal systemic encephalopathy (PSE) index developed by Conn *et al*., is currently widely used.[19] However, the Food and Drug Administration (FDA) strongly objected to the use of this system and favoured the adoption of a detailed mental status evaluation system for hepatic encephalopathy.[1] Further, clinical trials using a new mental state evaluation system, which satisfies the FDA's requirements, is required to confirm the efficacy of rifaximin for the treatment of hepatic encephalopathy.

CONCLUSION

The study did not confirm improved efficacy of lactulose plus rifaximin as compared to lactulose alone in treating hepatic encephalopathy.

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