

EVALUATION OF EFFICACY OF RIFAXIMIN IN THE TREATMENT OF HEPATIC ENCEPHALOPATHY IN PATIENTS WITH CIRRHOSIS

Hafsa Habib¹, Dur-e Nayab¹, Zafar Hayat¹, Shahid Jamil¹, Habibullah Khan²

¹Department of Medicine, Khyber Teaching Hospital, Peshawar, Pakistan

²Department of Medicine, Gomal Medical College, D.I.Khan, Pakistan

ABSTRACT

Background: Cirrhosis is a major cause of mortality and morbidity worldwide. It is also a frequent cause of hospital admissions. The objective of this study was to determine the efficacy of rifaximin and lactulose versus lactulose alone for the treatment of hepatic encephalopathy.

Material & Methods: This randomized controlled trial was conducted at Medical Unit A, Khyber Teaching Hospital, Peshawar, Pakistan. Duration of the study was six months August 12, 2014 to February 11, 2015 in which a total of 122 patients were observed with 61 patients in each group. Consecutive, non-probability sampling technique was used for sample collection.

Results: Our study shows that mean age of the patients in Group A (rifaximin plus lactulose) was 50 ± 2.31 years, while mean age of the patients in Group B (lactulose alone) was 52 ± 2.78 years. In Group A 48% patients were males and 52% patients females while in Group B 45% patients were males and 55% females. Regarding the efficacy, rifaximin plus lactulose was effective in 45(74%) patients while lactulose alone was effective in 32(53%) patients with hepatic encephalopathy.

Conclusion: Lactulose plus rifaximin orally is more effective than lactulose alone in the treatment of acute hepatic encephalopathy.

KEY WORDS: Liver Cirrhosis; Rifaximin; Lactulose; Hepatic encephalopathy.

This article may be cited as: Habib H, Nayab D, Hayat Z, Khan H. Evaluation of efficacy of rifaximin in the treatment of hepatic encephalopathy in patients with cirrhosis. Gomal J Med Sci 2016; 14: 37-40.

INTRODUCTION

Cirrhosis is the irreversible scarring of liver after damage to the liver cells. It has many causes but an estimated 57% cases result from chronic hepatitis B and C virus infection.¹ Hepatic encephalopathy is a serious but potentially treatable complication of cirrhosis. It may be precipitated by certain factors like constipation, high protein diet, dehydration, electrolyte imbalance, upper gastro-intestinal bleeding, infection, renal impairment, hypoglycemia, porto-systemic shunts, and certain medications like narcotics and sedatives.² Overt HE occurs in approximately 30% patients of cirrhosis with significant morbidity and mortality.³⁻⁷

Corresponding Author:

Dr. Hafsa Habib

Department of Medicine

Khyber Teaching Hospital

Peshawar, Pakistan

E-mail: hafsahabibi85@hotmail.com

Most therapies for HE are directed at reducing nitrogenous load in the gut, an approach consistent with hypothesis that it results from systemic accumulation of gut-derived neurotoxins, especially ammonia, in patients with impaired liver function and porto-systemic shunting.⁸ Some oral antibiotics like neomycin, paromomycin, vancomycin, and metronidazole have been effectively used, with or without lactulose, to reduce the load of ammonia-producing enteric bacteria in patients with acute HE.⁹ Rifaximin is a minimally absorbed oral antimicrobial agent with broad-spectrum against enteric bacteria. According to a study there was reversal of HE in 76% patients receiving rifaximin and lactulose vs. 50.8% in those receiving lactulose alone.¹⁰ In various other studies, the combination of rifaximin and lactulose has been shown to be more effective than lactulose alone in the treatment of HE.^{11,12}

There are many international studies on the effectiveness of rifaximin in the treatment of HE but

none from our part of the world. Assessment of efficacy of rifaximin and lactulose on the outcome of acute HE in our setup will help in the better management of these patients. The objective of this study was to determine the efficacy of rifaximin and lactulose vs. lactulose alone for the treatment of hepatic encephalopathy.

MATERIAL AND METHODS

This was a randomized Controlled Trial, conducted in Medical Unit A, Khyber Teaching Hospital, Peshawar, Pakistan, over six months August 12, 2014 to February 11, 2015. The sample size was 122 calculated by "WHO Sample size determination in health studies" software; with P1, efficacy of rifaximin and lactulose of 76% and P2, efficacy of lactulose alone of 50.8%.¹⁰ To show the superiority of the first regime with a statistical power of 90% and Confidence interval of 95%. Total patients were 122 with 61 patients in each group. Sampling technique was consecutive, non-probability sampling. Inclusion criteria were Patients of both genders with age 18-60 years, having an established diagnosis of cirrhosis liver with grade 2, 3 or 4 HE. Exclusion criteria were intercurrent infection, renal impairment (serum creatinine >2.0 mg/dl), hepatoma, upper GI bleed, taken Rifaximin in the last 3 months.

After approval from the Hospital Ethical Committee, patients fulfilling the inclusion/exclusion criteria were recruited, among cirrhosis patients admitted in Medical Department for HE. Written informed consent was taken from relatives of patients. Detailed history and physical examination was performed. Investigations like, full blood count, liver function tests, serum creatinine, and serum electrolytes (Na⁺, K⁺) was performed at the base-line. Patients were randomly allocated to one of the two groups on lottery basis. Group A receiving rifaximin 550 mg twice daily along with lactulose 30 ml three times daily orally and Group B receiving only lactulose 30 ml three times daily orally. Patients were graded for hepatic encephalopathy on West Haven criteria at the time of enrollment and at day 7. The above mentioned information was recorded in a proforma. The data was entered and analyzed in SPSS version 16.0. Frequency and percentages were calculated for categorical variables like gender, and encephalopathy grading. Mean + standard deviation were calculated for continuous variables like age. Chi square test was applied to compare the efficacy of both the treatments. P-value < 0.05 was considered as significant. Also, the efficacy was stratified for age groups, gender, and baseline encephalopathy grade to see the effect of modifiers. Results were presented as Tables and Graphs.

RESULTS

A total of 122 patients (61 patients in each group) were observed to determine the efficacy of rifaximin plus lactulose versus lactulose alone for the treatment of hepatic encephalopathy. The mean age of patients in Group A was 50±2.31 years and the mean age of patients in Group B was 52 years with SD ± 2.78. Regarding gender 29(48%) patients were males and 32(52%) patients were females. Whereas in Group B 27(45%) patients were males and 34(55%) patients were females.

The baseline severity of hepatic encephalopathy was recorded as in Group A 21(35%) patients had Grade II hepatic encephalopathy, 28(45%) patients had Grade III, and 12(20%) patients had Grade IV

Table 1: Baseline severity of hepatic encephalopathy (n=122).

Severity of Hepatic Encephalopathy	Group A	Group B
Grade II	21(35%)	18(30%)
Grade III	28(45%)	30(48%)
Grade IV	12(20%)	13(22%)
Total	61	61

Group A: rifaximin 550 mg + lactulose 30 ml, Group B: lactulose 30 ml

Table 2: Severity of hepatic encephalopathy after follow-up (n=122).

Severity of hepatic encephalopathy	Group A	Group B
Grade I	27(45%)	21(35%)
Grade II	18(30%)	25(40%)
Grade III	15(24%)	13(22%)
Grade IV	1(1%)	2(3%)
Total	61	61

Group A: rifaximin 550 mg + lactulose 30 ml, Group B: lactulose 30 ml Chi Square test was applied in which P value was 0.003

Table 3: Efficacy (n=122).

Efficacy	Group A	Group B
Effective	45(74%)	32(53%)
Not effective	16(26%)	29(47%)
Total	61	61
Total	61	61

Group A: Rifaximin 550 mg + Lactulose 30 ml, Group B: Lactulose 30 ml Chi Square test was applied in which p-value was 0.003.

hepatic encephalopathy. Where as in Group B 18(30%) patients had Grade II hepatic encephalopathy, 30(48%) patients had Grade III, and 13(22%) patients had Grade IV hepatic encephalopathy. (Table 1)

Severity of hepatic encephalopathy after follow-up was analyzed as in Group A 27(45%) patients had Grade I hepatic encephalopathy, 18(30%) patients had Grade II, 15(24%) had Grade III, and one (1%) patient had Grade IV hepatic encephalopathy. Where as in Group B 21(35%) patients had Grade I hepatic encephalopathy, 25(40%) patients had Grade II, 13(22%) had Grade III and 2(3%) patients had Grade IV hepatic encephalopathy. (Table 2) The efficacy was analyzed as rifaximin plus lactulose was effective in 45(74%) patients while lactulose alone was effective in 32(53%) patients. (Table 3)

DISCUSSION

In our study the mean age of the patients in Group A (rifaximin + lactulose) was 50 ± 2.31 years while the mean age of patients in Group B (lactulose) was 52 ± 2.78 years. In Group A 48% patients were males and 52% females while in Group B 45% patients were males and 55% females.

Rifaximin plus lactulose 30 ml was effective in 74% patients while lactulose alone was According to a study there was reversal of HE in 76% patients receiving rifaximin and lactulose vs. 50.8% in those receiving lactulose alone.⁷ In various other studies, the combination of rifaximin and lactulose has been shown to be more effective than lactulose alone in the treatment of HE.¹³⁻¹⁶

In study conducted by Sharma et al¹⁰ a total of 120 patients (mean age 39.4 ± 9.6 years; male/female ratio 89:31) were included in the study, 30.8% patients were in Child-Turcotte-Pugh (CTP) class B and 69.2% in CTP class C. Mean CTP score was 9.7 ± 2.8 and the MELD (Model for End-stage Liver Disease) score was 24.6 ± 4.2 . At the time of admission, 18.3% patients had grade 2, 33.3% had grade 3, and 48.3% had grade 4 HE. There was a significant decrease in mortality after treatment with lactulose plus rifaximin vs. lactulose and placebo (23.8% vs. 49.1%, $p < 0.05$). There were significantly more deaths in group B because of sepsis (group A vs. group B: 7:17, $p = 0.01$), whereas there were no differences because of gastrointestinal bleed (group A vs. group B: 4:4, $p =$ non-significant (NS)) and hepatorenal syndrome (group A vs. group B: 4:7, $p =$ NS). Patients in the lactulose plus rifaximin group had shorter hospital stay (5.8 ± 3.4 vs. 8.2 ± 4.6 days, $p = 0.001$).

In another study conducted by Sarin et al¹⁷ a significantly greater percentage of patients in the

combination group experienced a reversal of HE compared to lactulose (70% vs. 50%, $p = 0.003$). Combination of rifaximin and lactulose also significantly reduced the length of hospital stay (6 days vs. 8 days, $p = 0.001$) and mortality rate (20% vs. 50%, $p < 0.05$) compared to lactulose alone. Overall, combination therapy of rifaximin and lactulose appeared to be more effective than lactulose.

CONCLUSION

Lactulose plus rifaximin orally is more effective than lactulose alone in the treatment of acute hepatic encephalopathy.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

GRANT SUPPORT AND FINANCIAL DISCLOSURE

None declared.

AUTHORS' CONTRIBUTION

Conception and Design:	HH, ZH, HK
Data collection, analysis and interpretation:	HH, DN, ZH, HK
Manuscript writing:	HH, DN, ZH, HK