

Research Article

Mean Blood Ammonia Level After Treatment With Rifaximin Versus Neomycin In Chronic Liver Disease Patients Presenting With Hepatic Encephalopathy

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Abstract |

Objective: To compare Rifaximin versus neomycin in chronic liver disease (CLD) patients presenting with hepatic Encephalopathy.

Methodology: This Randomized controlled trial was conducted at North Medical Ward, King Edward Medical University/ Mayo Hospital Lahore from June to December 2013. Total 100 patients of CLD with Hepatic Encephalopathy were included through non-probability, purposive sampling and were named group A & B by random division. In Group A, patients received conventional Antibiotic Neomycin 3000mg 6-hourly daily while in Group B; patients received Rifaximin 600mg 12-hourly daily orally for 21 days. Blood Ammonia levels of both groups after 21 days treatment were analyzed by the software SPSS version 16.

Results: The mean age of patients was 54.23 ± 13.70 years with 54 (54%) male and 46 (46%) females. Out of 54 male patients, 28 (52%) were randomized to Rifaximin and 26 (48%) were randomized to Neomycin. Similarly, out of 46 female patients, 22 (48%) were randomized to Rifaximin and 24 (52%) were randomized to Neomycin. The serum Ammonia level after treatment with Rifaximin was 58.00 (14-117) g/dl whereas with Neomycin was 87.00(38-381) g/dl. Significant difference was found between both groups (p -value<0.0001).

Conclusion: Rifaximin is a better treatment option in CLD patients with Hepatic Encephalopathy as compared to conventional Neomycin.

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Introduction

Chronic liver disease (CLD) is a process of progressive destruction and regeneration of hepatocytes leading to hepatic fibrosis and cirrhosis.¹ One of the most important complication of this disease is Hepatic Encephalopathy (HE) which is manifested as confusion, impaired consciousness and ultimately coma.² 20% CLD patients develop HE annually, and

at any time about 30–45% CLD patients present with HE. On formal neuropsychological testing its prevalence is 60–80%.³

HE occurs as a result of shifting of portal blood into the systemic blood through portosystemic collaterals. Its pathogenesis is also explained by neurotoxins ammonia, which is produced in gut of cirrhotic patients & enters circulation reaching brain.⁴ Accu-

mulation of ammonia in brain can be precipitated by many factors like constipation, diarrhea, hypoglycemia, upper gastrointestinal bleeding, infections etc. There are so many drugs that have been used in HE treatment. One of the agent, a synthetic antibiotic Rifaximin, is very effective in management as well as prevention of recurrences.^{5,6} Major side effects are diarrhea and dehydration.⁷ Neomycin is an alternative antibiotic used for patients intolerant or nonresponsive to non-absorbable disaccharide Rifaximin. Major side effects are nausea, vomiting, ototoxicity & nephrotoxicity.^{8,9} The current literature is limited and controversial regarding comparison of both of these drugs. The rationale of this study was to evaluate rifaximin as a better treatment alternative to neomycin in HE.

Methodology

This Randomized controlled trial was done at North Medical Ward, King Edward Medical University/ Mayo Hospital, Lahore from June to December 2013. After ethical approval, sample size of 100 patients (Decompensated CLD Patients with grade 2 or 3 HE of both genders with age 30-80 years) was taken by Non-probability purposive sampling & calculated with 95% confidence level, 80% power of test and taking mean blood ammonia level i.e. 78.6 ± 20.3 $\mu\text{mol/L}$ with Rifaximin and 118.2 ± 40.1 $\mu\text{mol/L}$ with neomycin in CLD patients of HE. After taking written consent & demographic details, these patients were randomly divided into 2 groups A & B by using lottery method. In Group A, patients received conventional Antibiotic Neomycin 3000mg 6-hourly orally daily for 21 days while in Group B, patients received Rifaximin 600mg 12-hourly orally daily for 21 days. Blood Ammonia levels were assessed in both groups after 21 days of treatment from the K.E Medical university laboratory. However Pre-treatment Baseline blood ammonia level was not measured; a limitation in this study.

Comparative analysis was done using SPSS version 16. Quantitative variables such as age, post treatment ammonia level were presented as mean \pm SD. Qualitative variables such as gender was presented as frequency and percentage. Shapiro-Wilk test was applied to check whether outcome variable (ammonia level) followed- normal distribution. Mann-Whitney U test was applied to compare median blood

ammonia level after treatment in both groups. P-value<0.05 was considered as significant. Confounders were controlled through stratification of age and gender applying Mann-Whitney U test taking p-value<0.05 as significant.

Results

The mean age of the patients in both groups was 54.23 ± 13.70 years whereas the minimum and maximum ages of the study patients were 30 and 85 years respectively. The mean age of the patients randomized to Rifaximin was 54.52 ± 15.22 years whereas in Neomycin group, it was 53.94 ± 12.15 years. There were 55 (55%) patients of age 30-55 years while 45 (45%) were of age 56-80 years

(Table 1). There were 54 (54%) male and 46 (46%) females. The male to female ratio was noted as 1.17:1. Out of 54 male patients, 28 (52%) were randomized to Rifaximin and 26 (48%) were randomized to Neomycin. Similarly, out of 46 female patients, 22 (48%) were randomized to Rifaximin and 24 (52%) were randomized to Neomycin. (Fig. 1)

The value of test of normality was significant showing that the values of outcome variable (ammonia level) are not following normal distribution. So, we calculated median and range of outcome variable and compared in both groups by applying Mann Whitney U test. The serum Ammonia level after treatment with Rifaximin was 58.00(14-117) g/dl whereas with Neomycin was 87.00(38-381) g/dl. There was significant difference found between both groups (p-value<0.0001). Among the patients of age 30-55 years, the serum Ammonia level after treatment was 63.00(31-117)g/dl with Rifaximin whereas was 101.00(46-310)g/dl with Neomycin. There was significant difference found between both groups (p-value=0.002). Among the patients of age 56-80 years, the mean serum Ammonia level after treatment was 54.00(14-97)g/dl with Rifaximin whereas was 79.00 (38-381) g/dl with Neomycin. There was significant difference found between the two groups (p-value = 0.025). Moreover, patients of age 55-80 years have more reduction in ammonia level as compared to patients of age 30-55 years. Among males, the mean serum Ammonia level after treatment was 65.00 (14-117) g/dl with Rifaximin whereas was 87.00(38-381) g/dl with Neomycin. There was significant difference

found between the two groups (p -value=0.003). Among females, the mean serum Ammonia level after treatment was 56.5 (34-91)g/dl with Rifaximin whereas was 87.00 (46-310) g/dl with Neomycin. There was significant difference found between the two groups (p -value=0.001). Moreover, females had more reduction than males. (Table 2)

Table 1: Baseline Characteristics of the Patients

	Rifaximin	Neomycin	Total
n	50	50	100
Age (years)	54.52±15.22	53.94±12.15	54.23±13.70
Age 30-55	27 (54%)	28 (56%)	55 (55%)
Age 56-80	23 (46%)	22 (44%)	45 (45%)

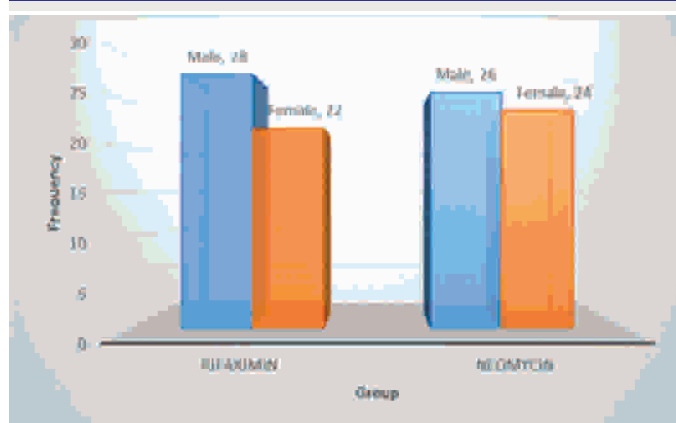


Fig 1: Distribution of Gender of Patients in both Groups

Table 2: Serum Ammonia Level after Treatment in both Groups

	Rifaximin	Neomycin	p-value
n	50	50	
Ammonia level after treatment	58.00(30)	87.00(73)	<0.0001
Age 30-55	63.00(37)	101.00(78)	0.002
Age 56-80	54.00(24)	79.00(30)	0.025
Sex: Male	65.00(34)	87.00(60)	0.003
Sex: Female	56.50 (25)	87.00(85)	0.001

Discussion

HE is a common complication of CLD with a wide spectrum of neuropsychiatric symptoms ranging from mild cognitive impairment to death.^{10,11} The key factor in its pathogenesis is circulating ammonia toxin & HE is reversible after treatment.¹² Currently newer antibiotic Rifaximin has been prescribed but with little clinical data. On the other hand conventional antibiotic Neomycin has efficacy similar to previously used non-absorbable sugar molecule, lactulose in many clinical trials.^{13,14}

Traditionally, non-absorbable disaccharides & oral antibiotics have been used as the first-line treatment for HE. Although safe, but the need to adjust disaccharide doses to achieve two to three loose bowel movements per day, often leads to frequent nausea, vomiting, and flatulence and affects compliance.^{15,16} Other Poorly absorbed oral antibiotics such as Neomycin, vancomycin or paromomycin are considered more effective than disaccharides with fewer side effects like deafness, kidney & brain dysfunction and bacterial resistance.^{3,17-20}

On the other hand, Rifaximin is a newer agent is more effective in treating HE without severe side effects. It is well tolerated and has lesser chances of bacterial resistance although expensive.²¹ It was first used in Italy in 1987 and has recently been approved in the United States for prevention as well as treatment of HE.^{3,8,22,23}

Although in our study, baseline ammonia level was not measured, so it is difficult to explain that, which drug has more decrease in serum ammonia level. This was the limitation of our study. However, the final response comparing both the drugs, it was much more reduction in serum ammonia levels by Rifaximin as compared to Neomycin.

Conclusion

There was a significant decrease in end point mean blood ammonia level with Rifaximin as compared to neomycin group. Hence Rifaximin is better choice in reducing higher blood ammonia levels as compared to Neomycin in patients of HE. Thus in our study we have resolved the controversy in use of two drugs & will use Rifaximin in future for treating HE. However baseline serum ammonia level being the limitation of this study, it is recommended that further trials should be conducted to check the efficacy of the two drugs.

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