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Research Article

Evaluation of Rifaximin in Preventing Recurrence of Hepatic Encephalopathy in Cases of Chronic Liver Disease

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ABSTRACT

Objective: To evaluate the recurrence of hepatic encephalopathy in cirrhotic patients treated with Rifaximin plus Lactulose versus conventional oral treatment with Lactulose alone.

Materials & Methods: Total 100 cases (50 for treatment group and 50 placebo group) of chronic liver disease with hepatic encephalopathy having age 20-60 years either male or female were selected for this cross sectional study from Department of Medicine, DG Kahn Hospital DG Khan from March 2017 to September 2017.Rifaximin Tablet 550 mg twice daily along with standard prescription i.e. Lactulose 30 to 60 ml in two to three divided doses per day was prescribed to treatment group. Conventional treatment i.e. Lactulose 30 to 60 ml in two to three divided doses per day was prescribed to placebo group.

Results: Age range in this study was from 20 to 60 years with mean age of 43.68 ± 10.87 years.The mean age of patients in treatment group was 43.76 ± 10.54 years and in placebo group was 43.65 ± 11.13 years. Recurrence of hepatic encephalopathy was seen in 09 (18%) patients in treatment group and 22 (44%) patients in placebo group with p-value of 0.005

Conclusion: This study concluded that rifaximin plus lactulose is better in reducing the recurrence of hepatic encephalopathy as compared to conventional treatment with lactulose alone.

Keywords: Hepatic encephalopathy, lactulose, rifaximin, recurrence.

INTRODUCTION:

Hepatitis C Virus (HCV) is a leading cause of chronic liver disease affecting an estimated 170 million people worldwide.[1] Hepatic encephalopathy (HE) represents a continuum of transient and reversible neurologic and psychiatric dysfunction in patients with chronic liver disease. [2] Hepatic encephalopathy occurs in approximately 30%–45% of patients with cirrhosisshowing great burden on hospitals[3]. Treatment strategies are directed towards increased elimination and reduction of gut-derived ammonia in addition to correction of conditions that provoke hepatic encephalopathy. Lactulose, nonabsorbable synthetic disaccharide syrup, is digested by bacteria in the colon to short-chain fatty acids, resulting in acidification of colon contents. This

acidification favors the formation of ammonium ion in the $NH_4NH_3 + H^+$ equation; NH_4^+ is not absorbable, whereas NH_3 is absorbable and thought to be neurotoxic. Lactulose also leads to a change in bowel flora so that fewer ammonia-forming organisms are present.[1,2] Although lactulose seems to work in the acute setting, but for durability of remission different antibiotics have to be used.[4-7]

Oral antibiotics with systemic absorption like vancomycin, neomycin, paromomycin, and metronidazole have been used to reduce the burden of ammoniform gut flora but not recommended for long term use because of nephrotoxicity, ototoxicity, and peripheral neuropathy.[4]Rifaximin is a poorly absorbed antibiotic that is thought to reduce ammonia production by eliminating ammonia-producing colonic bacteria with no systemic manifestations. 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.[4-6] Many small studies have suggested that rifaximin is effective in treating acute HE and is extremely well tolerated but few studies are available showing long term remission [4] and none is available for Pakistani population. In a study done to determine long term remission of HE by Rifaximin, rate of recurrence of HE came out 22.1% of patients in the rifaximin group, as compared with 45.9% of patients in the placebo group. A total of 13.6% of the patients in the rifaximin group had a hospitalization involving hepatic encephalopathy, as compared with 22.6% of patients in the placebo group (P=0.01).[4]

Overt episodes of hepatic encephalopathy are debilitating, can occur without warning, render the patient incapable of self-care, and frequently result in hospitalization. Although the occurrence of episodes of hepatic encephalopathy appears to be unrelated to the cause of cirrhosis, increases in the frequency and severity of such episodes predict an increased risk of death.[8-9]Rifaximin has shown promising results in preventing the recurrent episodes of hepatic encephalopathy[4,5] Pakistani population is different from others in dietary habits and gut flora due to different consumption of meat when compared to western population[7], a major factor in ammonia production. If this study showed better results in terms of prevention of hepatic encephalopathy by the combined use of Rifaximin and Lactulose, it might help us to reduce mortality in Chronic Liver Disease patients secondary to Hepatic Encephalopathy and decrease burden of indoor patients in our overloaded hospitals.

Research Methodology:

After approval from local ethical review committee and informed consent, total 100 cases (50 for treatment group and 50 placebo group) of chronic liver disease with hepatic encephalopathy having age 20-60 years either male or female were selected for this cross sectional study from Department of Medicine, DG Kahn Hospital DG Khan from March 2017 to September 2017.

The patients with expectation of liver transplantation within 1 month after the screening visit, The presence of conditions that are known precipitants of hepatic encephalopathy:

a. Gastrointestinal hemorrhage within 3 months before the screening visit
b. Chronic renal insufficiency (creatinine level, >2.0 mg per deciliter)
c. Respiratory insufficiency
d. Anemia (hemoglobin level, <8 g per deciliter)
e. An electrolyte abnormality (serum sodium level, <125 mEqper liter; serum calcium level, >10 mg per deciliter [2.5 mmol per liter]; or potassium level, <2.5 mmol per liter)
f. Inter-current infection, or active spontaneous bacterial peritonitis[4]were excluded from the study.

Rifaximin Tablet 550 mg twice daily along with standard prescription i.e. Lactulose 30 to 60 ml in two to three divided doses per day was prescribed to treatment group. Conventional treatment i.e. Lactulose 30 to 60 ml in two to three divided

doses per day was prescribed to placebo group. All patients were discharged from ward after hepatic encephalopathy Conn's score will be <2. Enrolled patients were followed for 3 months at which final outcome i.e. recurrence of hepatic encephalopathy (yes/no) was noted. All this data was recorded on a predesigned proforma.

OPERATIONAL DEFINITIONS:

- Chronic Liver Disease: CLD was diagnosed on ultrasonography with small size liver (size<13 cm) having coarse texture liver and having one of the following in addition:
  - Portal vein diameter >10mm.
  - Splenomegaly: size of spleen (length)> 13 cm on ultrasound.
  - Ascites: shifting dullness +ive and confirmed on ultrasound.
- Hepatic Encephalopathy: Hepatic encephalopathy was assessed by Conn score[107] (based on history and clinical examination) as follows;

0 = no personality or behavioral abnormality on clinical assessment.

1 = Day-night sleep pattern disturbance (contrary to patient's previous sleeping routine, he or she remains awake during night and sleeps in the morning), impairment of ability to add or subtract (unable to sequentially subtracting 7 starting from 100).

2 = Disorientation in time (at least three of the followings are wrong: day of the month, day of the week, month, season or year), obvious personality changes, flapping tremors in hands (on clinical assessment).

3= Disoriented also for space (considered positive if patient wrongly reported city or place), responsiveness only on stimulus.

4 = coma (non-responsiveness even to painful stimuli).

Hepatic Encephalopathy was taken as positive if Conn's score will be ≥2.

Recurrence: was taken as positive if patient of hepatic encephalopathy of Conn's score ≥2 was presented again within 3 months after discharge from ward with Conn's score <2.

Data was analyzed by using SPSS version 18. Mean and SD was calculated for numerical data and frequencies were calculated for categorical data.

RESULTS:

Age range in this study was from 20 to 60 years with mean age of 43.68 ± 10.87 years.The mean age of patients in treatment group was 43.76 ± 10.54 years and in placebo group was 43.65 ± 11.13 years. Recurrence of hepatic encephalopathy was seen in 09 (18%) patients in treatment group and 22 (44%) patients in placebo group with p-value of 0.005 as shown in Table 1.

Duration of disease was >6 months with mean duration of 10.69 ± 6.86 months. The mean duration of disease in treatment group was 10.87 ± 6.72 months and in placebo group was 10.28 ± 6.60 months. In ≥6 – <12 months duration of disease group, recurrence of HE was observed in 06 (17.64%) patients and 16 (44.44%) patients respectively in treatment group and placebo group and the difference was statistically significant with p valaue 0.016. In >12 months duration of disease group, recurrence was noted in 04 (25%) patients and 06 (42.86%) patients respectively in treatment group and placebo group but the difference was statistically insignificant with p value 0.139. (Table 2)

Patients were divided into 4 age group, in age group 20-30 years, recurrence of HE was noted in 02 (28.57%) patients and 03 (37.50%) patients in treatment and placebo group and the difference was statistically significant (P = 0.714). In 31-40 years age group, recurrence was found in 03 (25.0%) patients of treatment group and in 07 (58.33%) patients of placebo group but the difference was not significant with p value 0.098. In age group 41-50 years, 02 (14.29%) patients of treatment group and 04 (33.33%) patients of placebo group reported with recurrence of HE. But insignificant difference of recurrence was observed with p value 0.250. In age group 51-60 years, recurrence of HE was reported in 02 (11.76%) patients and 08 (44.44%) patients respectively in treatment group and placebo group

and the difference was statistically significant with p value 0.031. Table 3

Total 07 (19.44%) male patients of treatment group and 15 (45.45%) patients of placebo group were reported with recurrence of HE and the difference was significant with p value 0.021. Recurrence of HE was observed in 02 (14.29%) female patients of treatment group and 07 (41.18%) patients of placebo group but the difference was not significant with p value 0.101. Table 4

Table 1: Comparison of efficacy between both groups for female patients

Group	Recurrence HE		Total	P value
	Yes	No		
(Treatment)	09 (18%)	41 (82%)	50	0.000
(Placebo)	22 (44%)	28 (56%)	50	

Table 2: Stratification of Recurrence of HE in both groups with respect to duration of disease.

Duration of disease (months)	Treatment group		Placebo group		p-value
	Recurrence of HE		Recurrence of HE		
	Yes	No	Yes	No	
≥6 – <12	06 (17.64 %)	28 (82.35 %)	16 (44.44 %)	20 (55.56 %)	0.016
>12	04 (25%)	12 (75%)	06 (42.86 %)	08 (57.14 %)	0.139

Table 3: Stratification of Recurrence of HE in both groups with respect to age of patients.

Age of patients	Treatment group		Placebo group		p-value
	Recurrence of HE		Recurrence of HE		
	Yes	No	Yes	No	
20-30	02 (28.57%)	05 (71.43%)	03 (37.50%)	05 (62.50%)	0.714
31-40	03 (25.0%)	09 (75.0%)	07 (58.33%)	05 (41.67%)	0.098
41-50	02 (14.29%)	12 (85.71%)	04 (33.33%)	08 (66.67%)	0.250
51-60	02 (11.76%)	15 (88.24%)	08 (44.44%)	10 (55.56%)	0.031

Table 4: Stratification of Recurrence of HE in both groups with respect to Gender.

Gender	Treatment group		Placebo group		p-value
	Recurrence of HE		Recurrence of HE		
	Yes	No	Yes	No	
Male	07 (19.44%)	29 (80.56%)	15 (45.45%)	18 (54.55%)	0.021
Female	02 (14.29%)	12 (85.71%)	07 (41.18%)	10 (58.82%)	0.101

DISCUSSION:

Many treatment options are available for patients with hepatic encephalopathy, but no evidence currently supports the treatment of hepatic encephalopathy. Most patients show clinical signs of improvement in the symptoms of hepatic encephalopathy within 24–48 h of initiation of treatment (both empiric therapy and treatment of the underlying causes). Serum levels of ammonia might lag behind the clinical response. However, if hepatic encephalopathy persists after 72 h of treatment, the following possibilities must be explored: other causes of encephalopathy might have been missed or inadequately treated; a precipitating factor might have been missed, treated inadequately or remain uncorrected; effective empiric therapy has not been instituted or has been given to excess.[10]

In our study, recurrence of hepatic encephalopathy was seen in 09 (18.37%) patients in treatment group and 22 (40.90%) patients in placebo group with p-value of 0.005. In a study done to determine long term remission of HE by Rifaximin, rate of recurrence of HE came out 22.1% of patients in the rifaximin group, as compared with 45.9% of patients in the placebo group. A total of 13.6% of the patients in the rifaximin group had a hospitalization involving hepatic encephalopathy, as compared with 22.6% of patients in the placebo group (P=0.01).[4]Rifaximin, by contrast, has emerged as an effective treatment strategy to prevent recurrence of hepatic encephalopathy in a multicenter study published in 2010.[11]

Rifaximin proved effective compared to placebo in 299 patients with recurrent encephalopathy (HE) who were in remission. Rifaximin 550 mg twice daily did recue the risk of an episode of hepatic encephalopathy (HR 0.42; 95% CI [0.250-0.64]) as well as the risk of hospitalization from hepatic encephalopathy (HR 0.50; 95% CI [0.29 – 0.87]).[112]

Rifaximin is a broad spectrum antibiotic with Gram negative, Gram positive, aerobic, and anaerobic bacteria coverage. It possesses a low incidence of systemic side effects because it is poorly absorbed and also has a low incidence of inducing bacterial resistance. Previously, rifaximin's only approved indication was for the treatment of travelers' diarrhea caused by Escherichia coli at a dose of 200 mg three times daily. Recently, it has been indicated for use in reducing the risk of recurrent HE at a dose of 550 mg twice daily.[13]

A double-blind, randomized, dose-finding, multi-center study examined rifaximin at doses of 600 mg, 1200 mg, and 2400 mg daily for tolerability and safety in the treatment of HE. Results indicated improvement in patients and found rifaximin was best tolerated at the 1200 mg per day dose.[13]

CONCLUSION:

This study concluded that Rifaximin plus Lactulose is better in reducing the recurrence of hepatic encephalopathy as compared to conventional treatment with Lactulose alone. So, we recommend that Rifaximin plus Lactulose should be used as a primary treatment method in hepatic encephalopathy for reducing its recurrence.

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