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Research Article

Comparison of recurrence of hepatic encephalopathy between rifaximinplus lactulose versus conventional oral treatment with lactulose alone

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ABSTRACT

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

Materials & Methods:
This cross sectional study was conducted at Department of Medicine, Bahawal Victoria Hospital, Bahawalpur from March 2017 to September 2017. Total 200 patients of HE were selected and two groups were made i.e. treatment group and placebo group. Recurrence of HE was assessed between the both groups.

Results: Total 200 patients of HE were selected for this study and recurrence of HE was compared. Mean age of the patients was 44.78 ± 11.87 years, mean age of patients of treatment group was 44.33 ± 10.45 years and mean age of placebo group was 43.33 ± 10.13 years. Comparison of recurrence of HE was done between treatment group and placebo group. Recurrence of HE was found in 22 (22%) cases of treatment group and 47 (47%) cases of placebo group. Recurrence of HE was significantly (P = 0.000) higher in placebo group as compared to treatment group.

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, non absorbable 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.[4-6]

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.[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.

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[10] (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 was ≥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.

MATERIAL AND METHODS

This cross sectional study was conducted at Department of Medicine, Bahawal Victoria

Hospital, Bahawalpur from March 2017 to September 2017. Total 200cases of chronic liver disease with duration of liver at least 6 month, either male or female having age from 20-60 years were selected for this study. Exclusion criteria was: the expectation of liver transplantation within 1 month after the screening visit. The presence of conditions that are known precipitants of hepatic encephalopathy (Gastrointestinal hemorrhage within 3 months before the screening visit, Chronic renal insufficiency (creatinine level, >2.0 mg per deciliter), Respiratory insufficiency, Anemia (hemoglobin level, <8 g per deciliter), 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), Inter-current infection, or active spontaneous bacterial peritonitis[4]).

Patients randomly divided into two groups i.e. treatment and placebo groups for the study using random numbers generated from random table. Treatment group patients were advised to take tab Rifaximin 550 mg twice daily along with standard prescription i.e. Lactulose 30 to 60 ml in two to three divided doses per day. Placebo group was prescribed only conventional treatment i.e. Lactulose 30 to 60 ml in two to three divided doses per day. All patients were discharged from ward after hepatic encephalopathy Conn's score was<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.

Data collected was entered and analyzed in the SPSS version 19. Mean and SD was calculated for numerical data and frequencies and percentages were calculated for categorical data.

RESULTS

Total 200 patients of HE were selected for this study and recurrence of HE was compared. Mean age of the patients was 44.78 ± 11.87 years, mean age of patients of treatment group was 44.33 ± 10.45 years and mean age of placebo group was 43.33 ± 10.13 years. Comparison of recurrence of HE was done between treatment group and placebo group. Recurrence of HE was found in 22 (22%) cases of treatment group and 47 (47%) cases of placebo group. Recurrence of HE was significantly (P = 0.000) higher in placebo group as compared to treatment group. (Table 1) In 6-12 months of duration of HE group, in treatment group recurrence was noted in 14 (19.44%) patients and in 35 (46.47%) patients of placebo group. The difference of recurrence rate was statistically significant between treatment group and placebo group with p value 0.000. In >12 months duration of HE group, recurrence of HE was found in 6 (21.43%) patients of treatment group and in 13 (52%) patients of placebo group and the difference was statistically significant with p value 0.025. (Table 2) Stratification in relation to age was done. Among the patients of age group 20-30 years, in treatment group recurrence of HE was 5 (26.32%) and in placebo group was 20 (50%) but difference was not statistically significant with p value 0.190. In age group 41-50 years, recurrence was found in 5 (26.32%) patients of treatment group and in 25 (41.67%) patients of placebo group and the difference was significant with p value 0.020. (Table 3) Higher (45.45% vs 21.92%) recurrence was found in placebo group as compared to treatment group in male patients and the difference was significant with p value 0.000. Among female patients, recurrence was found in 5 (18.82%) cases of treatment group and in 13 (43.75%) cases and the difference was significant with p value 0.013. (Table 4)

Table 1 Comparison of recurrence of HE between treatment and placebo group

Group	Recurrence of HE		P value
	Yes (%)	No (%)	
Treatment	22 (22)	78 (78)	0.000
Placebo	47 (47)	53 (53)	

Table 2 Stratification in relation to duration of disease

Duration of disease	Treatment group		Total (%)	Placebo group		Total (%)	p-value
	Recurrence of HE			Recurrence of HE			
	Yes (%)	No (%)		Yes (%)	No (%)		
6 – 12 months	14 (19.44)	58 (80.56)	72 (72)	35 (46.47)	40 (53.33)	75 (75)	0.000
>12 months	6 (21.43)	22 (78.57)	28 (28)	13 (52)	12 (48)	25 (25)	0.025

Table 3 Stratification in relation to age

Age of patients	Treatment group		Total (%)	Placebo group		Total (%)	p-value
	Recurrence of HE			Recurrence of HE			
	Yes (%)	No (%)		Yes (%)	No (%)		
20-30	05 (26.32)	14 (73.68)	38 (38)	20 (50)	20 (50)	40 (40)	0.190
41-50	04 (13.33)	26 (86.87)	62 (62)	25 (41.67)	35 (58.33)	60 (60)	0.020

Table 4 Stratification in relation to gender

Gender	Treatment group		Total (%)	Placebo group		Total (%)	p-value
	Recurrence of HE			Recurrence of HE			
	Yes (%)	No (%)		Yes (%)	No (%)		
Male	16 (21.92)	57 (78.08)	73 (73)	32 (45.45%)	35 (54.55%)	67 (67)	0.000
Female	5 (18.82)	22 (81.48)	27 (26)	13 (43.75%)	20 (56.25%)	33 (33)	0.013

DISCUSSION

In our study, recurrence of hepatic encephalopathy was seen in 22 (22%) patients in treatment group and 47 (47%) patients in placebo group with p-value of 0.000. 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.[10] Patients who had previously experienced at least two episodes of hepatic encephalopathy and were in remission were randomly assigned to receive either rifaximin or placebo and were followed up for 6 months. More than 90% of participants in this study were treated with lactulose in addition to rifaximin or placebo. The patients in the rifaximin group maintained their remission from hepatic encephalopathy more effectively than did patients in the placebo group, and rifaximin was associated with improved tolerability and decreased adverse effects compared with placebo. Rifaximin is, therefore, likely to dominate treatment strategy for hepatic encephalopathy in the future. [10]

The controversy of using rifaximin either in place of or in addition to lactulose has waged on despite current practice guidelines that recommend lactulose as first-line treatment. 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]). Of note, over 90% of patients in each arm were on baseline lactulose and upon sub-group analysis, those

patients who were not using lactulose at baseline had no significant differences in outcomes with rifaximin compared to placebo. Overall, treatment was well tolerated and rifaximin had positive outcomes.[11]

Probably the most common prescribing method is the use of rifaximin with lactulose. A study by Sharma et al demonstrated this by comparing lactulose alone to lactulose plus rifaximin. This study evaluated 120 patients with overt HE (>80% grade 3 or 4) who were randomized to receive either lactulose alone or lactulose plus rifaximin. Baseline Child-Pugh was mainly Class B and C and Mean MELD was 24.5 ± 4.2. Of these patients, 55 had experienced previous episodes of HE requiring treatment, but no patients were refractory to treatments. There were more patients in the combination therapy group that experienced reversal of HE symptoms within a 10 day period (76% vs. 44% lactulose alone; p = 0.004).[12]

Other studies have shown rifaximin is as effective and possibly superior than conventional therapies such as lactulose and is well tolerated. However, there is still a lack of evidence to support rifaximin as sole therapy for HE and the cost of rifaximin greatly exceeds the cost of lactulose. With the available data and the updated guidelines from the AASLD, the recommendation is still lactulose as first choice for the treatment of HE or for prevention of recurrent HE episodes after initial episode and rifaximin as effective add-on therapy.[13-14]

A prospective, randomized, double-blind, placebo-controlled trial was conducted in 94 patients with HE. Rifaximin was administered at a dose of two 200 mg tablets (400 mg) three times daily for 8 weeks in the rifaximin group (n= 49) and two placebo tablets were similarly administered in the control group (n=45). The primary outcome measured was the reversal of HE defined as reduction in mean number of abnormal NP tests at 8 weeks. Secondary outcomes were the reversal of HE at 2 weeks and the improvement in SIP score at 8 weeks. Rifaximin showed a significant reduction in the mean number of abnormal NP scores compared to baseline at 2 and 8 weeks. [15]

A randomized, double-blind, controlled trial of 120 patients compared combination rifaximin 400 mg three times daily and lactulose 30-60 mL twice daily (n=63) with lactulose 30-60 mL twice daily (n=57) to evaluate the efficacy and safety of combination therapy versus monotherapy for the treatment of HE. Patients included in this study had either been treated with lactulose for HE episodes in the past or were currently receiving lactulose as prophylactic therapy. The primary outcome was the complete reversal of HE episode according to the West Haven criteria, and secondary endpoints were mortality and length of hospital stay. A significantly greater percentage of patients in the combination group experienced a reversal of HE compared to lactulose (76% vs. 44%, p=0.004).[16]

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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