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RIFAXAMIN VS LACTULOSE; IN IMPROVING CIRRHOTIC PATIENTS WITH HEPATIC ENCEPHALOPATHY

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ABSTRACT… Objectives: To compare Rifaxamin and Lactulose in improving the grades of hepatic encephalopathy in patients with decompensated liver disease. **Study design:** Randomized controlled trial comparing the use of rifaxamin and Lactulose. **Place and duration of study:** 1st July 2014 to 30th June 2015 in Department of Medicine, Aziz Bhatti Shaheed Teaching Hospital Gujarat. **Results:** 1st July 2014 to 30th June 2015 in medical department of Aziz Bhatti Shaheed Teaching Hospital Gujarat. **Results:** 400 cases were divided in two equal groups: Group A took Rifaximin & Group B Lactulose. Improvement in grades of hepatic encephalopathy were calculated on weekly bases. Monitoring was done by checking blood ammonia levels, number connection tests, flapping tremors and mental status. 40 patients (10%) did not stay in ward for one week. In ninety percent etiology of decompensated liver disease was hepatitis C virus. Improvement was noted in 76.96% (n=137) in Group-A and 72.52% (n=132) in Group-B, p value was found insignificant (>0.05). **Conclusions:** Rifaximin and lactulose had similar efficacy in the treatment of mild to moderate hepatic encephalopathy.

Key words: Hepatic encephalopathy, rifaximin, lactulose, comparison

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INTRODUCTION

Hepatic encephalopathy (HE) is a reversible neuropsychiatric syndrome associated with chronic and acute liver dysfunction. It is characterized by cognitive and motor deficits of varying severity. Early symptoms include reversal of sleep pattern, apathy, hypersomnia, irritability, and personal neglect that progresses to delirium, drowsiness and coma along with neurologic signs including hyperreflexia, rigidity, myoclonus, and asterixis.[1] HE usually signals advanced liver failure, and is often considered a clinical indicator for liver transplantation.[2] Proper management of HE requires identification and treatment of the precipitating factors that include infections, GI bleed, electrolyte disorder, diuretic overuse, constipation and may be unidentified in fraction of patients.[3,4]

Hepatic encephalopathy has been reported in 19% to 50% of patients who are admitted with cirrhosis.[5] Although the occurrence of episodes of hepatic encephalopathy appears to be unrelated to the cause of cirrhosis[6], increases in the frequency and severity of such episodes predict an increased risk of death.[7] The treatment of HE is focused on reducing both the production and absorption of gut-derived ammonia, in patients with impaired liver functions and Porto systemic shunting.[8]

Presently, non-absorbable disaccharides and antibiotics are the mainstay of therapy. Lactulose is currently the drug of choice for HE treatment. Lactulose is preferred because its cathartic effect is more predictable, its formulation is more convenient and its less sweet taste.[9] Side effects include excessive diarrhea, nausea, abdominal pain and flatulence that often limit compliance to therapy. Rifaximin is a derivative of rifampin. It is a minimally absorbed antimicrobial agent which is effective against gram-positive, gram-negative, aerobic and anaerobic enteric bacteria.[10] Rifaximin looks like an ideal drug for the treatment of HE without adverse effects.

Some studies concluded that rifaximin is superior to lactulose and antimicrobials in patients suffering from mild-to-moderate severe HE.[11], but a larger meta-analysis of twelve studies comparing rifaximin to conventional oral therapy failed to prove any significant difference between the two drugs.[12]

Most of the meta analysis were done in western world where major cause of cirrhosis is alcohal[13] while in our population major culprit is viral hepatitis.[14] Moreover, the microflora in the gut in our populations differ from that of western populations.[15] If rifaximin is found to be effective in the local population, it would help in managing this disease. The aim of this study was to compare the efficacy and safety of Rifaximin with lactulose in the local population for the prevention of secondary attacks of hepatic encephalopathy.

PATIENTS AND METHODS

The objective of the study was to compare the improvement in grades and episodes of hepatic encephalopathy with lactulose compared to rifaximin. This was a randomized controlled trial which was carried out in department of medicine, Aziz Bhatti Shaheed Teaching hospital, Gujarat from 1st July 2013 to 30th June 2015. The severity of hepatic encephalopathy was graded with the West Haven Criteria.[3] Improvement in HE was measured as at least 1 grade reduction in presenting stage of hepatic encephalopathy after 7 days from start of treatment.

A total of 400 patients with HE above age 30 years were included in the study after taking informed consent. They were divided in two groups randomly; Group A; 200 patients who took Rifaxamin 550mg twice a day and Group B; 200 patients who were given Lactulose 30-90ml per day.

The sample size was calculated through WHO statistical calculator according to the prevalence of disease with absolute precision of 10%. Patients having age 30-70 years of both genders with decompensated cirrhosis and hepatic encephalopathy (grade 1 to 3) were included in study. Patients with major psychiatric illness, chronic renal insufficiency (creatinine > 2x normal), respiratory insufficiency, taking sedatives, allergic to rifamycin or disaccharides were excluded from study. Pregnant or lactating women were also not included in study.

All basic demographic information (name, age, sex, address and contacts) were noted after an informed consent. Patients after getting admission in ward were assessed to measure the baseline hepatic encephalopathy grades and then followed up till seven (7) days. After 7 days, all patients were appraised again for grades of hepatic encephalopathy and their improvement. 40 patients (twenty two from group A and 18 from group B) left the ward before completing one week of treatment. Blood ammonia levels and Number connection test (NCT) were performed before and at the end of treatment. Flapping tremors and mental status was checked on daily basis. All this information was recorded through pre-designed Performa.

The collected data was analyzed statistically by using SPSS version 16. Quantitative variables like age was presented in form of mean±S.D. Qualitative variables like gender, improvement in HE grade was presented in form of frequency and percentage. Chi-square was used to compare frequency of improvement in HE grade in both groups. P-value of $\leq$ 0.05 was considered as significant.

RESULTS

400 patients fulfilling the inclusion/exclusion criteria were enrolled to compare the improvement in hepatic encephalopathy grades with Rifaximin and Lactulose.

Age distribution of the patients was done which shows that 39%(n=78) in Group-A and 43%(n=86) in Group-B were between 30-50 years of age while 61%(n=122) in Group-A and 57%(n=114) in Group-B were between 51-70 years of age, mean±sd was calculated as 45.82±14.72 and 45.24±14.75 years respectively. (Table-I)

Age (in years)	Group-A (n=200)		Group-B (n=200)	
	No. of patients	%	No. of patients	%
30-50	78	39	86	43
51-70	122	61	114	57
mean±sd	45.82±14.72		45.24±14.75	

Table-I. Age Distribution (n=400)

Gender distribution of the patients was done which shows that 51% (n=102) in Group-A and 48% (n=96) n Group-B were male while 49% (n=98) in Group-A and 54% (n=54) in Group-B were females. (Table-II)

Gender	Group-A (n=200)		Group-B (n=200)	
	No. of patients	%	No. of patients	%
Male	102	51	97	48.50
Female	98	49	103	51.50

Table-II. Gender Distribution (n=400)

Etiology of cirrhosis was hepatitis C in 90% (360) of the patients, while Hepatitis B was found in 5% (20), Alcohlic liver disease in 2% (8), Willson's disease 0.5% (2), haemochromatosis in 0.5% (2), autoimmune hepatitis in 0.5% (2), However in 6 patients 1.5% exact etiology was not found.

Forty patients (10%), 22 of group A and Eighteen of group B left the ward before completing one week so they were excluded from study. Comparison of improvement in grades of hepatic encephalopathy with Rifaximin and Lactulose revealed improvement in 76.96% (n=137) in Group-A and 72.52 % (n=132) in Group-B while 23.04% (n=41) in Group-A and 27.48 % (n=50) in Group-B did not show any improvement, p value was calculated as insignificant >0.05. (Table-III)

Improvement	Group-A (n=178)		Group-B (n=182)	
	No. of patients	%	No. of patients	%
Yes	137	76.96	132	72.52
No	41	23.04	50	27.48

Table-III. Improvement in grades of hepatic encephalopathy with rifaxamin verses lactulose in patients presented with decompensated cirrhosis (n=360)
P value=> 0.05

DISCUSSION

Lactulose and rifaximin are commonly used therapy in patients who have experienced an episode of hepatic encephalopathy. However, long-term use of lactulose is limited by its side effects. Therefore, rifaximin is emerging as a first-line drug to reduce the frequency of recurrent hepatic encephalopathy. In this study we compared the Rifaximin and lactulose in improving the grades of hepatic encephalopathy for seven days after admission. In 90% of the patients cause of cirrhosis was hepatitis C, which is present in approximately 10 million people in Pakistan.[16]

In this study, 76.96% (n=137) patients in Group-A reveals improvement from the presenting grades of hepatic encephalopathy while 72.52% (n=132) in Group-B showed improvement, p value was calculated as >0.05 which was insignificant. Results showed that both drugs have almost similar benefits to patients. Similar results were found by Paik et al[17], who compared rifaximin and lactulose for management of HE. It was observed that HE grades was improved in 81.3% with rifaximin while 72.7% with lactulose and grades of ammonia level was improved in 78.1% with rifaximin while 59.1% with lactulose after 7 days of drug administration. There was an insignificant difference between both groups (p-value>0.05).

A metaanalysis by Jiang et al. and review by Zullo concluded that Rifaximin is not superior to lactulose in treatment of chronic HE[18,19]

In a study from Sheikh Zayd hospital Lahore, Rifaximin was failed to reduce the risk of recurrent hepatic encephalopathy during a 6 months period. [20]

Lawrence KR and colleagues[21] recorded that Rifaximin was effective in improving behavioral, laboratory, mental status, and intellectual abnormalities associated with hepatic encephalopathy. Leevy CB et al[22] found rapid improvement in clinical features of encephalopathy during treatment with rifaximin compared with nonabsorbable disaccharides (lactulose, lactitol). Rifaximin treated patients

had shorter duration of hospitalization and less hospital charges compared with lactulose-treated patients.

In summary, our study showed that rifaximin and nonabsorbable disaccharides had similar outcomes in patients with hepatic encephalopathy. We suggest that therapy should be started with lactulose because of its lower cost and rifaxinmin should be reserved for patients who have severe adverse effects of disaccharides therapy.

CONCLUSION

Rifaximin and non-absorbable disaccharides had similar efficacy in the treatment of mild to moderate hepatic encephalopathy.

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"In life you are either a passenger or a pilot, it's your choice."

Unknown

AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Dr. Irfan Younis	Concept and design of study, Statistics manuscript writing, Data collection	
2	Dr. Zamir Butt	Critical revision of article, Statistics	
3	Dr. Malik Irfanullah Yasir	Data collection, Drafting of article	
4	Dr. Syed Muhammad Ali Shah	Criticle revision of article	