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STUDY TO KNOW THE RIFAXIMIN EFFICACY IN HEPATIC ENCEPHALOPATHY PREVENTION IN CIRRHOSIS OF LIVER

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Abstract:

Objective: *To evaluate the safety and efficacy of Rifaximin in patients with liver cirrhosis to prevent hepatic encephalopathy recurrence according to lactulose alone.*

Study design: *Randomized controlled trial.*

Location and duration: *In the Gastroenterology department of Bahawal Victoria Hospital, Bahawalpur for the Period of one year from May 2016 to May 2017.*

Methodology: *We had hepatic encephalopathy reports for approximately 4 weeks of liver cirrhosis to randomly receive selected rifaximin. 550 mg twice daily dose in 196 patients received (99 patient) or only lactulose (97 patients). They asked or found patients to take oral medication twice a day for 6 months until they experienced HE's recurrence.*

RESULTS: *Hepatic encephalopathy reduces recurrence over a period of significant six months, when compared with lactulose alone. Hepatic encephalopathy was suddenly present in 19 (19.19%) of the patients taking rifaximin, compared with 49 (50.51%) patients in the lactulose group. Hepatic encephalopathy was admitted in 12.6% (8) of the patients in the rifaximin group and 23.8% (15) in the total lactulose group, compared to the disease. 79 patients (79.79%) in the rifaximin group and 48 patients (49.48%) in the lactulose group had hepatic encephalopathy during the study period. In the majority of patients with advanced HE, 21-25 was the MELD score was in both groups. In both groups Death rate and morbidity rate was same.*

Conclusion: *Treatment with rifaximin at a 6-month period was more effective than lactulose alone in maintaining hepatic encephalopathy remission. In our study, rifaximin reduced hospitalization frequency significantly in patients with hepatic encephalopathy.*

Key words: *Hepatic encephalopathy, Rifaximin, Liver cirrhosis.*

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INTRODUCTION:

The common complication of liver cirrhosis is Hepatic encephalopathy (HE) which has a detrimental effect on survival and survival related to health. It is the term used to explain the variable changes and complex in neuropsychiatric symptoms and symptoms that aggregate diseases of liver. Hepatic encephalopathy recurrent attacks are debilitating, may require multiple admittance to Hospitals and make the patient unable to perform daily living activities. The increasing number and intensity of these sections increase the risk of mortality. The pathogenesis of these events is not clear. It plays an important role in both hepatocellular failure and portosystemic shunt development. Intestinal-associated toxins, especially ammonia, not detoxify by Liver and cross the blood-brain barrier, astrocytes than detoxify ammonia. The end result is minor cerebral edema, which affects fuctions of neurons. The purpose of the treatment was to minimize the amount of ammonia obtained from the intestine, to increase the ammonia cleanliness and to control the triggers. Lactulose is the standard treatment, while oral antibiotics are only associated with toxic effects when used in long walks. Rifaximin, a structurally related synthetic antimicrobial with rifaximin, has a wide spectrum of activity against gram-negative, gram-positive and enteric anaerobic bacterial strains and the risk of developing bacterial resistance is low. Systemic distribution is not important (4%). At least much effective as lactulose and antimicrobials which are non-absorbable, eg neomycin for hepatic encephalopathy treatment. In randomized trials, rifaximin, as well as lactulose, have been found to be more effective in preventing common attacks of hepatic encephalopathy. While in the western world the study population cirrhosis is mostly caused by Alcohol, In our country liver cirrhosis is due to viral hepatitis. In addition, in the eastern population gut micro flora may be distinct from the western population. Rifaximin in our influenza has a different response than in the west. In the local population if it is found effective, it helps to reduce the disease morbidity. The aim of this study is to assess the rifaximin safety and efficacy in the local people to avoid recurrent hepatic encephalopathy attacks.

METHODOLOGY:

It is a comparative study. Patients who have two past episodes at least of hepatic encephalopathy within the previous six months with a cirrhosis of any age and any gender and a criterion of West Haven Stage 0 or 1, and who received 25 or less points within the model OPD or who entered the room the last stage of the liver disease scale was included in the study. Patients who are admitted with diuretic use hepatic spontaneous bacterial peritonitis, active (PAS), encephalopathy (HE), potassium at a level of <2.5 mmol / l or with gastrointestinal bleeding, interstitial infection, electrolyte imbalance and constipation. These conditions have been corrected; however, he acknowledged that this section led to the second section of the HE Haven criteria at least in the last 6 months ≥ 2. Patients with known rifaximin, a calcium level of> 10 mg / dl, hepatocellular carcinoma and patients with additional problems such as chronic renal disease, cerebrovascular insufficiency and respiratory hypersensitivity injury are excluded. Information was provided about the illness work and its results and informed consent was obtained to participate in the study. The patient underwent a history and clinical examination during enrollment. Any anomalies were found 1 score: HE first story, clinic (0 points are assessed using West Haven criteria, insignificant awareness, attention deficit and abbreviated anxiety score 2: drowsiness, irrelevance and score 3 for disorientation ,stupor, drowsiness, confusion : For coma score 4). The MELD score is calculated. The patient is required to take medication twice a day for 6 months or until the sudden encephalopathy sudden onset of development or until another reason is required to withdraw the drug. Patients were asked to develop harmful events, including pneumonia, recurrent infections, bacterial peritonitis or varicose veins leading to HE, such as cutting off the study medication. Simultaneous administration of lactulose was allowed during the study. After randomization and screening, patients were asked to visit Gastroenterology and liver clinic for 7 days and up to 168 days for every 4 weeks. Phone monitoring was done on weekdays without going to the polyclinic. Safety assessments were made at each visit to a specific infection, including respiratory and gastrointestinal tract infections. The data were analyzed using Statistical Social Science Package (SPSS) version 20.

RESULTS:

196 total patients were randomized for the study. Most of the patients had hepatitis C-associated cirrhosis. The initial features were same. Most of the patients have 41-65 age group and the distribution by sex was similar in both groups. In both groups, the majority of patients had 11-20 MELD score given in table 1.

Table 1: *Basic Demographics.*

	Lactulose Group (n = 97)	Rifaximin Group (n = 99)
Age in years		
<50	60	66
≥50	37	33
Mean ± SD	44.45 ±3.43	43.97 ± 3.54
Gender		
Male	47 (48.45%)	46 (46.46%)
Female	50 (51.54%)	53 (53.53%)
Range of MELD score		
0 - 10	8 (8.24%)	9 (9.09%)
11 - 20	51 (52.57%)	49 (49%)
21 - 25	38 (39.17%)	41 (41.41%)
Mean ± SD	17.74 ± 2.98	15.45 ± 3.45
Number of episodes of encephalopathy in the past		
2 episodes	45 (46.39%)	51 (51.51%)
> 2 episodes	52 (53.60%)	48 (48.48%)
Etiology of cirrhosis		
Hepatitis C	88 (90.72%)	87 (87.87%)
Hepatitis B	6 (6.18%)	5 (5.05%)
Ethanol	2 (2.06%)	3 (3.03%)
Other	1 (1.03%)	2 (2.02%)

MELD = Model for End Stage Liver Disease

At least one dose of study in all the patients received drug and at least after enrollment one safety evaluation was performed. During the first episode of hepatic encephalopathy medical study was stopped or if patients developed serious harmful events. Rifaximin did not use diuretic because nine patients in all and 8 patients in the other group did not all have ascites. However, diarrhea, abdominal pain or diarrhea occurred in 16 patients in the rifaximin group and 12 patients in the lactulose group experienced self medication with corticosteroid metronidazole and ciprofloxacin / levofloxacin section.

Table 2: *Subgroup analysis of patients free of PSE during trial.*

	Lactulose Group 48 (49.48%)	Rifaximin Group 79 (79.79%)	p-value
Age (in years)			
< 50	36 (75%)	58 (73.41%)	0.833
≥ 50	11 (25%)	21 (26.5%)	
GENDER			
Male	22 (45.83%)	37 (46.83%)	0.913
Female	26 (54.17%)	42 (53.16%)	
Range of MELD score			
0 – 10	6 (12.5%)	6 (7.59%)	0.633
11 – 20	37 (77.08%)	63 (79.74%)	
21 – 25	5 (10.41%)	10 (12.65%)	
Number of episodes of encephalopathy in the past			
2	21 (43.75%)	43 (54.43%)	0.275
> 2	27 (56.25%)	36 (45.56%)	

All patients were admitted to study drug use, and follow-up gastroenterology visits were excluded in the open air, one patient in each group lost follow-up. 97 patients in the break over section lactulose group were reported in 99 patients and 49 (50.51%) and 19 (19.19%) in the treatment group. The difference was significant with p <0.001 (Table III).

Table 3: *Subgroup analysis of patients with breakthrough PSE.*

Total	Control Group 49 (50.51%)	Treatment Group 19 (19.19%)	p-value < 0.001
Age (in years)			
	49	19	0.418
< 50	25 (51.02%)	07 (36.84%)	Insignificant
≥ 50	24 (48.97%)	12 (63.15%)	
Gender			
Male	21 (42.85%)	11 (57.85%)	0.270
Female	28 (57.14%)	07 (42.10%)	Insignificant
Range of MELD score			
0 – 10	1 (2.04%)	0	0.290
11 – 20	16 (32.65%)	3 (15.78%)	Insignificant
21 – 25	32 (65.30%)	16 (84.21%)	
Number of episodes of encephalopathy in the past			
2	9 (18.38%)	07 (36.84%)	0.118
> 2	41 (83.67%)	12 (63.15%)	Insignificant

During the 6-month study period, there is a relative decrease in the ratio of ruptured episode to rifaximin by 57% compared to the lactulose group. The most frequent cause of HE in both groups was the progression of the disease (Table 4). In both groups, there were 16 patients with hepatic encephalopathy who were searched for all known triggers and none were available. In our study, an average increase in the MELD score of 9 in the lacquer group and 6 in the rifaximin group was observed in the PSE of these patients. A total of 8 (12.6%) patients in the rifaximin group admitted to the hospital with hepatic encephalopathy in 15 (23.8%) patients in the laculose group. The incidence of harmful events reported during the study was similar in both groups. Labor medicine Suspended when serious harmful events were reported. The great majority of adverse events were due to disease progression or cirrhosis complications and were treated according to prescribed care standards (Table 4).

Table 4: *Cause of PSE and adverse events and deaths.*

Causes of PSE	Control Group	Treatments Group
Constipation	11	8
Sepsis due to pneumonia	3	2
Hypokalemia due to overdiuresis	11	7
Progression of disease	21	15
SBP	8	6
SBP + HRS	3	3 (5.88%)
Variceal bleed	9	4
Acute on chronic hepatitis	6	3
Adverse events / deaths	-	-
Death due to persistent PSE	2 (18.18%)	1 (7.69%)
Death due to HRS	2 (18.18%)	2 (15.38%)
Death due to acute on chronic hepatitis	-	1 (7.69%)
Death due to pneumonia	1(9.09%)	1 (7.69%)
Death due to cellulitis	1(9.09%)	-
Death due to variceal bleed	1(9.09%)	2 (15.83%)
Abdominal pain	-	1 (7.69%)
Nausea and vomiting	2 (18.18%)	3 (23.08%)
Sore throat / fatigue	1(9.09%)	-
Gen. weakness	-	1 (7.69%)
Missing data	1(9.09%)	1 (7.69%)
Self – medication with other antibiotics	10/63 (15.8%)	4/63 (6.3%)

SBP = Spontaneous Bacterial Peritonitis; HRS = Hepato Renal Syndrome; PSE = Portosystemic encephalopathy.

Nausea / vomiting, widespread weakness, sore throat, and fatigue were removed after the study drug was discontinued. In the Lactulose group, and MELD rose from 16 to 34, leaving hepatitis E, study drug from chronic hepatitis E and on standardized treatment lines. During the study 14 deaths occur. 7 patients in the placebo group and 7 patients in the treatment group died. The majority of deaths were associated with disease progression or infection (Table 4). At the beginning of the study, all patients had one or more symptoms of decompensated cirrhosis, namely ascites, edema, or varicose vein, in addition to hepatic encephalopathy.

DISCUSSION:

Hepatic encephalopathy prevention encephalopathy manifestation is associated with a violation of a regimen of significant morbidity and a treatment regimen that leads to re-admission and poor outcome, especially in the treatment of patients with liver disease, an important goal quality of life. Our study had the most recent history of hepatic encephalopathy manifestation (≥ 2 episodes in the last 6 months) before inclusion of rifaximin. Hepatic encephalopathy in the remission period showed that hepatic encephalopathy reduced sudden episodes. In our study, rifaximin treatment alone was superior to lactulose treatment. In contrast, a recent local study of 126 disease treated with rifaximine showed that our study had no role in leaving hepatic encephalopathy frequency. Hepatic encephalopathy, which represents rifaximin therapy, is the risk of admission to the secondary hospital Clinical significance of our findings. Also, the risk of hospitalization in a low hospital means lower hospital costs. The incidence of side effects was the same in the rifaximin group and the lactulose group. With prolonged use of metronidazole, kidney, nausea and peripheral neuropathy associated with the use of ototoxicity and aminoglycosides (eg, neomycin and paromomycinase) are minimally reduced in patients with advanced hepatocellular disease. Bacterial resistance risk Rifaximin plasma levels Minimal because systemic antibiotic Rifaximin seems to be less. Resistant plasmids are also mediated by other antimicrobial agents, while a reversible resistance to rifaximin is achieved by Genomics. In vivo studies of Rifaximin effects in vitro and in commensal flora explain that resistant organisms have low viability of rifaxine. In summary, this study demonstrates an important protective effect of rifaximin against hepatic encephalopathic episodes. Rifaximin also reduces the risk of hospitalization in patients with hepatic encephalopathy.

CONCLUSION:

Over a period of 6 months, Rifaximin therapy protected the hepatic encephalopathy remission more effectively than the bladder. Rififaximin treatment has also significantly reduced the risk of hospitalization for hepatic encephalopathy.

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