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A RANDOMIZED TRIPLE BLIND, PLACEBO- CONTROLLED TRIAL TO DETERMINE EFFECTIVENESS OF RIFAXIMIN IN PREVENTING HEPATIC ENCEPHALOPATHY IN PATIENTS WITH CHRONIC LIVER DISEASE

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Abstract:

Objective: *To study the effectiveness of using rifaximin for prevention of recurrent hepatic encephalopathy (HE) attacks in patients with chronic liver disease (CLD).*

Methods: *This study was conducted at the hepatology department of Mayo Hospital, Lahore, during October 2014 to April 2015 by following randomized, triple blind, placebo-controlled trial. Total 126 patients of CLD, who during remission from hepatic encephalopathy were prescribed rifaximin 550mg, two times a day for six months or placebo was advised twice daily for six months. Patients were advised to either take drug from 6 months or till onset of hepatic encephalopathy episode. These prescriptions were advised after randomly dividing patients into two groups consisting of 63 each.*

Results: *The participants had mean age group 40.2 ± 2.3 years and 42.8 ± 4.5 years in test group and control group, respectively. Hepatitis C was found to be more common cause of cirrhosis as compared to hepatitis B. Forty out of 63 patients remained free from hepatic encephalopathy in test group while 35 patients did not suffer HE in control group during study period. Those who suffered HE had MELD scoring from 21 to 25 in both groups. There were similar adverse reactions and deaths in both groups.*

Conclusion: *Rifaximin has no effective role in preventing hepatic encephalopathy as compared to placebo.*

Key Words: *Hepatic encephalopathy, rifaximin, cirrhosis, placebo, chronic liver disease, recurrence.*

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INTRODUCTION:

Chronic liver disease is most commonly caused by hepatitis C. The hepatic encephalopathy is one of the life threatening complications in patients in liver cirrhosis. Repeated episodes of HE impairs patient's ability to perform routine tasks. It leads to repeated hospital admissions and increases risk of death [1,2,4].

Role of raised serum ammonia level in causing HE has been well explained in literature. Trials are under study to find the effective control of hepatic encephalopathy in CLD patients by either reducing GIT ammonia absorption, increased excretion of ammonia from body by using different agents. Lactulose is widely practiced for this purpose worldwide.[1,2] This study aims to evaluate the role of antimicrobials in reducing recurrent attacks of hepatic encephalopathy in CLD patients.

Rifaximin is a broad spectrum antimicrobial, used against both gram positive and gram negative bacteria. Its use in combination with lactulose for treating and preventing hepatic encephalopathy has been studied in several clinical trials. *Tapper EB, et al* in a systemic review published in March 2018 has elaborated the need to determine the better diagnostic tests with properly defined cutoff values to estimate the risk of MHE in patients with CLD.[3]

HEPACONTROL program has been studied in patients with CLD by *Morales BP, et al* in January 2018 and results were published in *international journal of gastroenterology and hepatology,* in which it was concluded that those patients who were followed up seven days after discharge and were frequently followed up later were prevented from hospital re admissions and fatal complications during first 60 days of discharge, than those who were not followed up. Thus HEPACONTROL can bring fruitful results in DCLD patients and can reduce hospital re admission rates, ultimately reducing health care cost and case fatality rate. [5]

The most common cause of liver cirrhosis in western world is alcohol intake, while in Pakistan the viral hepatitis is leading cause of liver cirrhosis. The gut flora is also different in developing world population as compared to developed nations. So, study results can be different in developing world in comparison to western world. This study aims to estimate the effectiveness of rifaximin in preventing HE in Pakistani population by keeping in view the abovementioned differences amongst developing and developed world and to help reducing morbidity and mortality rate.

METHODOLOGY:

This research was conducted at Mayo hospital Lahore from October 2014 to April 2015 after taking permission from hospital ethical committee. Inclusion criteria was CLD patients due to any cause with history of at least 2 hepatic encephalopathy episodes in last 6 months with more than 2 Conn score and end stage liver disease scale scoring of 25 or less, who visited either outdoor clinic or were admitted in ward. The patients with complications like hypokalemia, spontaneous bacterial peritonitis (SBP), gastrointestinal bleed, constipation were enrolled in study after these complications got settled. Patients with at least second episode of HE were included, Conn score in past 6 months was ensured to be more than 2. An exclusion criterion was patients who were hypersensitive to rifaximin and its derivatives, serum calcium >10mg/dl, hepato-cellular carcinoma, CVA (cerebrovascular accidents), ESRD (end stage renal disease. The purpose of research was well explained to all the patients and an informed written consent was taken from all of them.

At the time of enrollment into study the complete history and clinical examination was done and Conn scoring was used to assess past history.

Table: 1 Conn scoring.

Score 0	No abnormality found
Score 1	Short attention span
Score 2	Disoriented, lethargic, apathy.
Score 3	Confusion, stupor, somnolence
Score 4	Patient comatosed

After enrollment, patients were randomly divided into two subgroups, first one was test group in which rifaximin 550mg was given to all. The second group was placebo. Each pack was specially formulated by a pharmaceutical company on request. The placebo pack was labeled A while rifaximin pack was labeled B. Both tablets were of same shape, size and color. Both had similar packing. The company generated a code for this clinical trial and it was mentioned on packs that these drugs will be used for research purpose by following the ethical considerations. The code was destroyed after the completion of study by the company. The pharmaceutical company paid an honorarium to the principal investigator. No author holds any financial interest in company, neither company paid any remuneration to any author.

Patients were prescribed drug to be taken orally 12 hourly for 6 months, until the completion of duration or till they develop any breakthrough HE episode.

Breakthrough HE episode was defined as Conn score more than 2, either precipitated by constipation, electrolyte disturbance or disease progression. Patients and their attendants were well informed and properly counseled about the side effects of drugs and were advised to immediately report the doctor in case of appearance of any side effect or complication during the study period.

Patients who developed pneumonia, SBP, variceal bleed were advised to stop test drug. Lactulose was allowed to be taken by the patients. Neither patient, nor researcher or statistician had knowledge about the drug whether it was placebo or rifaximin. Follow up was advised on 7, 14 and 2 weeks thereafter out of 168 days. Telephonically patients were followed up later. Response to therapy was assessed by Conn scoring on day 0 and later on each follow up visit. A proforma was designed to collect the information.

SPSS version 20 was used to analyze data. For quantitative variables (age, MELD score) mean and SD was calculated. For qualitative variables (sex, previous episodes of HE, number of patients who suffered HE) frequency and percentages were calculated. Chi-square test and t-test were used to find the difference between two groups. Adverse events and deaths were summarized using descriptive statistics.

RESULTS:

126 patients participated in study. Hepatitis C was found to be the cause of CLD in majority of patients. Mostly patients had age group 41 to 69 years. Patients were divided randomly into two groups. The age and gender distribution was similar in both groups. MELD score was 11 to 20 in both groups.
After enrollment patients were given at least one dose of drug and safety profile was assessed once. Drug was stopped if patient developed HE episode or side effect or died. Lactulose, PPIs, calcium and vitamin D supplements were allowed to be taken during the study. Except three patients, all were on diuretics. The uninformed se of ciprofloxacin or levofloxacin or metronidazole was noted by 10 patients in placebo group and 4 in test group due to diarrhea, productive cough or abdominal pain. One patient was lost to follow-up, all others showed good compliance to prescribed drugs and were regularly followed up. 16 out of 63 patients in test group suffered HE and 14 out of 63 in placebo group suffered HE during study. Thus there was insignificant difference in both groups (p-value was 0.203).

All those patients who suffered HE were investigated for the possible precipitating event. Disease progression was found to be leading cause of HE episode in both groups. MELD score rise by 10 and 6 was noted in placebo and test group, respectively. Adverse events frequency was similar in both groups. The drug was stopped shortly after adverse event appearance. The cause of adverse events was disease progression which was managed according to the standard guidelines. Fewer side effects like nausea or vomiting, sore throat were resolved after treatment discontinuation. Abdominal pain in test group patients was evaluated for SBP which turned out to be negative and it resolved after drug discontinuation. Those who died in test group had billirubin level more than 2mg/dl and MELD score progressed from 17 to 35 amongst them. The lost to follow up patient had alcohol induced cirrhosis and he didn't stop alcohol use during treatment. A patient in control group suffered PSE, he had alcohol induced cirrhosis and disease was precipitated by binge intake. His billirubin rose from 1.8 to 20 mg/dl and MELD score to 30 from 16. Patient was advised to discontinue understudy drugs and to go through standard management protocols. Total 14 patients died during study, seven from each group. The cause of death was disease progression. All patients at the time of enrollment had either ascites, edema or active variceal bleed or any previous episode.

Table: 2 Basic characteristics.

	Test group	Placebo group
Age (years) Less than 65 More than 65 Mean ±SD	 53 10 42.8±4.5	 48 15 40.2±2.3
Gender Male female	 31 (41.2%) 32 (50.7%)	 29 (46%) 34 (53.9%)
MELD* score range 0 to 10 11 to 20 21 to 25 Mean ±SD	 2 (3.1%) 34 (53.9%) 27 (42.8%) 15.4 ±3.4	 5 (7.9%) 35 (55.5%) 23 (36.5%) 16.3 ±2.8
Cirrhosis etiology Hepatitis C Hepatitis B Alcohol others	 54 (85.7%) 6 (9.5%) 2 (3.1%) 1 (1.5%)	 50 (79.3%) 10 (15.8%) 2 (3.1%) 1 (1.5%)
Past encephalopathy episodes 2 More than 2	 30 (47.6%) 33 (52.3%)	 25 (39.6%) 38 (60.3%)

MELD* = Model for end stage liver disease.

Table: 3 Subgroup patient analysis free of PSE (portosystemic encephalopathy) during study.

	Test group	Placebo group	p-value
Age (years) Less than 65 More than 65 Mean ±SD	 30 (85%) 5 (14.3%)	 32 (80%) 8 (20%)	0.51
Gender Male female	 19 (54.2%) 16 (45.7%)	 19 (47.5%) 21 (52.5%)	0.55
MELD* score range 0 to 10 11 to 20 21 to 25 Mean ±SD	 2 (5.7%) 29 (82.8%) 2 (5%)	 5 (12.5%) 33 (82.5%) 2 (5%)	0.38
Past encephalopathy episodes 2 More than 2	 22 (62.8%) 13 (37.1%)	 17 (42.5%) 23 (57.5%)	0.07

DISCUSSION:

Rifaximin is broad spectrum antibiotic and its use for treatment of hepatic encephalopathy has been tested by many investigators. The lactulose and rifaximin combination treatment lead to rapid recovery in comparison to lactulose alone treatment. Crisafulli E, et al studied the abovementioned effect and concluded the work in favor of abovementioned hypothesis. [9,10]

According to a meta-analysis of 21 RCTs covering 2258 patients, published in journal of clinical and experimental hepatology in February 2017, it was concluded that there is mild effectiveness of using rifaximin in combination to lactulose in treating and preventing hepatic encephalopathy in patients suffering from CLD. [7]

By keeping in view the previous research data available on the under-study topic it has been noticed that some authors favors the effectiveness of rifaximin treatment for treating and controlling hepatic encephalopathy while some conclude it to be ineffective. Thus there is need to conduct more research work on a wider study sample to reach the conclusion. [6,8]

The current study aims in studying the effect of rifaximin in reducing the hepatic encephalopathy recurrence rate in Pakistani population. CLD due to viral hepatitis has been controlled in developed world by adopting safe transfusion techniques and improved injectable drugs protocols, but in developing countries like Pakistan the viral hepatitis load is still high and is the major cause of cirrhosis. Every 9th person in Pakistan is infected with hepatitis B or C virus, according to Punjab government communicable diseases screening survey, conducted in 2017. Thus CLD risk in Pakistani population is very high. In western world alcohol has replaced viral hepatitis in causing liver cirrhosis. Thus there is need to study effect of more drugs in preventing complications in CLD patients and to reduce treatment cost as well as mortality and morbidity rate.

CONCLUSION:

Rifaximin has no effective role in preventing hepatic encephalopathy as compared to placebo.

REFERENCES:

1- Ridola L, Nardelli S, Gioia S, Riggio O. How to design multicenter clinical trial in hepatic encephalopathy. *Journal of Clinical and Experimental Hepatology*. 2018.

2- Shawcross DL. Diagnosis and management of hepatic encephalopathy. *British Journal of Nursing* 2018; 27(3).

3- Tapper EB, Parikh ND, Waljee AK, Volk M, Carlozzi NE. Lok A. Diagnosis of hepatic encephalopathy: A systemic review of point-of-care diagnostic tests. *The American Journal of Gastroenterology*. 2018; 113: 529-538.

4- Ampuero J, Montoliu C, Simon-Talero M, Aguilera V, Millan A, Marquez C, et al. Minimal hepatic encephalopathy identifies patients at risk of faster cirrhosis progression. *Journal of Gastroenterology and Hepatology* 2018; 33(3): 718-725.

5- Morales BP, Planas R, Bartoli R, Morillas RM, Sala M, Casas I, et al. HEPACONTROL. A program that reduces early readmissions, mortality at 60 days, and healthcare costs in decompensated cirrhosis. *Digestive and Liver Disease* 2018; 50(1): 76-83.

6- Muhammad N, Khan MAR, Hussain A.Role of rifaximin in preventing the recurrence of hepatic encephalopathy in patients with chronic liver disease. P J H M S 2016;10(4): 1417-1420.

7- Kimer N, Gluud LL, Morris RW, Morgin MY. Rifaximin for the prevention and treatment of hepatic encephalopathy: A systemic review with meta-analysis with randomized controlled trials. *Clinical and Experimental Hepatology* 2017; 7(sup1): S78-S79.

8- Ferenci P, Runyon BA, Robson KM. Hepatic encephalopathy in adults, treatment. Up-to-date.2018.

9- Crisafulli E, Demma S, Rigano G, Bertino G. Treatment with rifaximin high dose plus lactulose vs rifaximin standard dose plus lactulose for acute hepatic encephalopathy in ED. *Journal of Hepatology* 2016; 64(2): S258.

10- Ali B, Zaidi YA, Alam A, Anjum HS. Efficacy of rifaximin in prevention of hepatic encephalopathy in patients with cirrhosis of liver. *Journal of College of Physicians and Surgeons Pakistan* 2014; 24(4): 269-73.