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COMPARISON OF RIFAXIMIN PLUS LACTULOSE WITH THE LACTULOSE ALONE FOR THE TREATMENT OF HEPATIC ENCEPHALOPATHY

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Abstract:

Hepatic encephalopathy is a stimulating complication of liver dysfunction. Therapeutic options for hepatic encephalopathy are currently limited and present significant risks and benefits associated with its use. Rifaximin is a new antimicrobial agent with a broad spectrum of activity that has shown promising results as an alternative option for liver encephalopathy.

Objectives and Objectives: *The present study was conducted in Mayo Hospital Lahore to compare the efficacy of rifaximin and lactulose as a combination against lactulose alone, to compare adverse effects and to study the rate of therapeutic effects of rifaximin and lactulose.****Methods:*** *it was a prospective observational study. 60 patients with hepatic encephalopathy (HE) have been studied. The patients were studied and treated according to the decision of the attending physician. At the time of the analysis, the patients were divided into 2 groups, the rifaximin group that received Rifaximin + Lactulose (R + L) and the Lactulose (L) group, which received only Lactulose. Parameters such as the degree of mental state, the degree of asterixis, the degree of serum ammonia, the degree of test for the numerical connection (NCT degree), the hepatic encephalopathy index (HE index) were assessed and compared in both groups. Clinical efficacy was determined using the HE index improvement. The primary endpoints were decreasing the HE index and reversing the HE ratings. Secondary endpoints were mortality from HE or any other cause, decreased mental status, asterixis grade, serum ammonia grade, NCT grade.****Results:*** *Of 60 patients, 32 received a combination of rifaximin + lactulose and 28 patients received lactulose only. The average Child-Turcotte-Pugh score (CTP score) was 10.6 in the R + L group and 10.32 in the L group. There was a statistically significant improvement in the degree of mental state, asterixis degree, serum ammonia degree , NCT grade, hepatic encephalopathy index in both groups, p-value <0.05, but there was no statistically significant difference between improved mental state grade, asterixis grade, serum ammonia grade, NCT grade, HE index between the two groups. Rifaximin the combination of lactulose was effective in 31 out of 32, i.e. 96.87% and lactulose alone in 24 out of 28 patients, or 85.71%, which is not statistically different, p = 0.3251.****Discussion:*** *the combination of rifaximin + lactulose is not superior to lactulose alone in the treatment of refractory liver encephalopathy. The addition of rifaximin may aid in the treatment of refractory liver encephalopathy****Conclusion:*** *the combination of rifaximin + lactulose is effective, but not superior to lactulose alone in the treatment of hepatic encephalopathy.*

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INTRODUCTION:

Hepatic encephalopathy is a syndrome observed in patients with cirrhosis Hepatic encephalopathy is defined as a spectrum of neuropsychiatric abnormalities in patients with hepatic dysfunction after the exclusion of other known brain diseases and is characterized by personality changes, intellectual deterioration and consciousness problems, it can seriously lead to coma and death. . 1 Ammonia has been implicated as a key molecule in the pathogenesis of the disease, due to its frequent increase in patients with cirrhosis and known cellular toxicity. 4 The clinical diagnosis of manifest liver encephalopathy is based on two simultaneous types of symptoms: impaired mental state , as defined by the Conn score (also called the West Haven criterion) (on a scale from 0 to 4, with higher scores indicating a more serious deterioration) and impaired neuromotor function2,3. Most hepatic encephalopathy therapies focus on treating episodes as they occur and are aimed at treating precipitating factors, reducing the nitrogen load in the intestine. In general, the oral antibiotics neomycin, paromomycin, vancomycin and metronidazole have been used effectively, with or without lactulose, to reduce a minimal amount of harmful bacteria in patients with hepatic encephalopathy.

Treatment with lactitol or non-absorbable lactulose disaccharides is the current standard of care for patients with hepatic encephalopathy, which reduces the absorption of ammonia through cathartic effects and altering the colon pH. Gastrointestinal acidification eventually inhibits the production of ammonia by coliform bacteria. An analysis of data from the hepato-biliary group Cochrane demonstrated the efficacy of lactulose on placebo, but did not show any survival benefit.5 Rifaximin is a semi-synthetic, non-systemic antibiotic, which is excreted almost exclusively in the stool as an unchanged drug. It was approved in late March 2010 by the FDA for the treatment of full-blown hepatic encephalopathy. By altering the flora in the gastrointestinal tract, rifaximin decreases intestinal production and ammonia absorption. Rifaximin has a broad spectrum of antibacterial activity and therefore can be an appropriate agent for eliminating anaerobic and aerobic colonic bacteria that are capable of producing ammonia but with a low risk of inducing bacterial resistance. 6 Rifaximin is well tolerated in almost all patient populations, including young children. No dose adjustment is necessary in patients with chronic liver disease or kidney failure. 6,11,13 With minimal systemic bioavailability, rifaximin may be more conducive to long-term use than other more bioavailable antibiotics with harmful side effects. It has been shown to prevent the HE episode and decrease the risk of hospitalization. 7 In randomized trials, rifaximin was more effective than non-absorbable disaccharides and had equivalent or greater efficacy than other antibiotics used in the treatment of acute HD 8.16 In a recent meta-analysis of 12 randomized controlled trials, Eltawil et al. . al.17 reported that rifaximin is as effective as other conventional oral agents for the treatment of HD with a better safety profile. But studies comparing the effectiveness of the combination of rifaximin and lactulose are limited. Therefore, the present study is conducted to compare the efficacy and safety profile of the combination of Rifaximin and Lactulose compared to Lactulose alone in the treatment of HD.

METHODS:

This is a non-randomized observational study conducted from January 2016 to July 2017at the tertiary care institution. After obtaining authorization from the institution's ethics committee, 60 HD manifest patients were enrolled who met the inclusion and exclusion criteria. All patients were studied and treated according to the attending physician. The duration of treatment ranged from 7 to 15 days until discharge or death in hospital. Each adverse event was recorded by specifying the starting time, duration and seriousness.

Study design:

HE severity was assessed according to West Haven criteria. The severity of cirrhosis was assessed by CHILD-PUGH-TURCOTTE (CPT) Score. The detailed anamnesis, the clinical and neurological examination was carried out in each patient. Routine investigations such as complete blood count, liver function test, kidney function test, serum electrolytes, blood sugar, prothrombin time and international normalized relationship were recorded. Details of special investigations such as USG Abdomen, Mr. Ammonia, brain CT, CXR, viral markers, ascites fluid analysis, hepatoportal Doppler have been recorded. Blood tests were performed on the day of admission (Day 1) and subsequently repeated in series from the day of admission to the final result. At the time of the analysis, the patients were divided into two groups:

Grade of Mental State:

Rifaximin + Lactulose, group (R + L) that received Rifaximin 1200 mg / day in 3 divided doses and Lactulose, 30–60 ml / three times a day, so that the patient goes from two to three semisoft stools in one day. Lactulose (L) group in which patients who

received lactulose 30 to 60 ml / three times a day so that the patient went from two to three semisoft stools in one day. Parameters such as the degree of mental state, the degree of asteressia, the degree of father mmia, the degree of numerical connection (NCT degree), the hepatic encephalopathy index (HE index) were estimated on day 1, day 3 and day (5-8) in both groups.

Degree of mental state:

This test is performed quantitatively using the Conn modification of the Parsons-Smith classification. Grade 0: no anomaly; Grade 1: trivial loss of consciousness, euphoria or anxiety, reduced attention span, reduced addition or subtraction performance; Grade 2: lethargy, disorientation with respect to time, evident change of personality, inappropriate behavior; Grade 3: semi-stupor drowsiness, sensitive to stimuli, confusion, severe disorientation, bizarr and behavior; and Grade 4: unable to evaluate mental function.

Table 1: Baseline characteristics of study patients

Parameter	Group A (n-32)	Group B (n-28)
Age in years	49.5 ± 9.7	53.9 ± 10.2
Male/ female	28/5	26/2
Etiology HBV/ HCV/Alcohol	5/4/23	5/4/15
CTP score (A/B/C)	1/6/25	1/9/18
HE grade 1/2/3/4	0/10/18/4	0/13/11/4
Mental status grade 1/2/3/4	0/10/18/4	0/10/15/3
HE index	13.31	12.96
T. bilirubin mg/dl	5.6	5.67
Albumin mg/dl	2.39	2.6
Creatinine mg/dl	1.46	1.39
INR	2.02	1.95
S. ammonia	172 ± 46.1	191.7 ± 60.4

The severity of the tremor flutter:
Severity was determined by extending the patients' arms and forearms with their wrists bent backwards for at least 30 seconds. We adopt a simplified classification system to minimize variations between observers. Grade 0: no movement of the flutter; Grade 1: rare flutter movement; Grade 2: continuous movement of the flutter; and grade 3: cannot be assessed.

Numerical connection test (NCT):
The time required to connect 25 progressive numbers, i.e. part A of the numerical connection test. Grade 0: <30 seconds (normal); Grade 1: 31-50 second; Grade 2: 51-80 seconds; Grade 3: 81-120 seconds; and grade 4:> 120 sec.

Ammonia levels in the blood:
Blood ammonia was measured before and after treatment with Cobas Integra 800 (Roche, Basel, Switzerland). Grade 0: <75 µM / L; Grade 1: 76-150 µM / L; Graduation 2: 151-200 µM / L; Grade 3: 201-250 µM / L; and grade 4:> 251 µM / L.

HE index:

The HE index was calculated from (Degree of mental state) X 3 + Degree of the connection test of Number + Degree of tremor of the flutter + Degree of ammonia in the blood The need for renal replacement therapy and inotropic support, upper gastrointestinal measuring cup, fresh frozen plasma support was also requested in both groups. Patient outcome and response to treatment were assessed using these parameters, relative to demographic factors, treatment received and any adverse effects. Efficacy was rated as improved, unchanged or worsened. A decrease in the HE index of at least 1 point was defined as improved and an increase in the HE index of one point or more was defined as worse. The duration of treatment was 7-15 days depending on the course and the result. The primary endpoints were a decrease in the HE index and a reversal of the HE degrees. Secondary endpoints were mortality from HE or any other cause, decreased mental status, asterixis grade, serum ammonia grade and NCT grade.

Statistical analysis:
Mental state degrees, serum ammonia degrees, NCT degree, flutter tremor degrees, HE degree and HE index were calculated. To compare the change in

degrees after treatment, an independent paired T test was used. To compare the variation of the degree of mental state, the serum ammonia levels, the NCT degree, the degrees of tremor at the flutter, the HE index after treatment in both groups, multivariate analysis of the variance test was applied . Fisher's exact test was used to learn about the improvement of HE scores and the HE index.

RESULTS:

A total of 74 patients with liver cirrhosis and liver encephalopathy (HE) were examined. Of these, 14 were excluded because they did not meet the inclusion criteria. 60 patients were included.The average age was 50.8 years and an ED of 10.07. The male / female ratio was 6.5: 1.32 patients (53.33%) received the Rifaximin + Lactulose (R + L) group,and 28 (46.66%) patients received only one lactulose (L) group. The etiology of cirrhosis was: 60% alcoholic, alcoholic with hepatocellular carcinoma 1.7%, alcoholic infection + HCV 1.7%, cryptogenetics 6.7%, cirrhosis related to HBV infection 16.7%, cirrhosis related to infection from HCV 13.3% of patients. Of the 60 patients, 23 (38.33%) were in grade 2 hepatic encephalopathy, 29 (48.33%) were in grade 3 and 8 (13.33%) of hepatic grade 4 Encephalopathy Of 60 patients, 46 had the first episode of hepatic encephalopathy and 14 had recurrent episodes. Of 60 patients, 2 had grade A child scores, 15 B patients, 43 C patients (Table 1).6 (10%) patients needed inotropic support and 54 (90%) did not. In 2 patients who needed inotropic support received rifaximin+ The combination of lactulose and 4 patients received lactulose only. 12 (20%) patients needed support for fresh frozen plasma and 48 (80%) did not need it. In patients who received fresh frozen plasma, 7 patients received rifaximin + lactulose and 5 patients received lactulose. In rifaximin+ Lactulose group, 3 had loose movements, 2 had pain in the abdomen, in the lactulose group 1 the patient had pain in the abdomen, 4 had loose movements.Baseline blood count, vital function test, kidney function test, serum electrolytes and arterial ammonia were comparable in both groups.

Recovery of HE:

HE scores improved in 31 out of 32, or 96.87% in the R + L group. In the lactulose group, HE improved in 24 out of 28 patients, or 85.71%, p-value 0.3251, or (Table3) not statistically significant. In our study, the degree of mental state improved from 1.81 to 0.22 (p = <0.05) in the R + L group and from 1.57 to 0.43 (p = <0.05) in the group L (Table 2); using an independent paired t test. The degree of asterixis improved from (Table 2) from 2.13 to 0.16 (p = <o, 05) in the R + L group and from 2.18 to 0.39 (p = <0.05) in the group L after treatment. In our study, after applying the independent t test, he demonstrated it; The degree of NCT improved from 3.84 to 1.75 (p = <0.05) in the R + L group and from 3.75 to 2.07 (p = <0.05) (Table 2) in the group L after the treatment. The degree of serum ammonia improved from 2 to 0.81 (p = <0.05) in the R + L group and from 2.36 to 1.11 (p = <0.05) in group L (Table 2) after treatment. In our study, after applying the independent t test, he demonstrated it; The pretreatment of the HE index was 13.31 and 12.96 respectively in the R + L group and in the L group. After treatment, the HE index improved to 3.56 in the R + L group and 4.86 in the L group. The P value is <0.05 in both cases (Table 2).

HE index improvement after treatment:

In our study, the hepatic encephalopathy index improved in 31 out of 32, or 96.87% in the R + L group. In the lactulose group it improved in 24 out of 28 patients, that is, in 85.71%. After applying the exact Fisher test, he showed that there were no statistically significant differences in the improvement of the HE index in both groups after treatment, P value (2 tails) 0.3251 (Table 3). 6 patients expired and 54 patients survived. There have been 2 deaths in Rifaximin + lactulose group and 4 in the lactulose group. The main causes of death were progressive liver encephalopathy, acute renal failure, hepatorenal syndrome, shock. Progressive hepatic encephalopathy represented 2 (33.33%) of deaths, hepatic encephalopathy + acute renal failure represented 1 (16.66%), hepatic encephalopathy + hepatorenal syndrome represented 2 (33.33%) of deaths, hepatic encephalopathy + hematemesis shock represented 1 (16.66%) of deaths. Adverse effects In the rifaximin + lactulose combination group, there were slow movements in 3 (9.3%) patients, abdominal pain in 2 (6.2) patients. There were no serious adverse effects in the rifaximin + lactulose group. 27 (84.5%) patients were free of side effects. In the lactulose group alone, loose movements occurred in 4 (14.3%) patients, pain in the abdomen in 1 (3.6%) patients. There were no serious adverse effects in this group. 23 (82.1%) patients were free of side effects. No patient withdrew from the study due to an undue side effect. The frequency of adverse effects was the same in both groups.

Table 2: Changes in HE index and related parameters post-treatment

Parameter	Rifaximin + Lactulose			P value	Lactulose			P value
	Day 1	Day 3	Day 5 - 8		Day 1	Day 3	Day 5 - 8	
Blood ammonia level (mmol/L)	172.53	-	130.97	<0.05	191.75	-	143.14	<0.05
Ammonia grade	2.0	1.59	0.81	<0.05	2.36	2	1.11	<0.05
Mental status grade	1.81±0.64	0.91	0.22±0.6	<0.05	1.57±0.69	0.82	0.43±0.9	<0.05
Grade of flapping tremor	2.12	1.06	0.16	<0.05	2.18	1.04	0.39	<0.05
Grade of NCT	3.84	3.44	1.75	<0.05	3.75	3.36	2.07	<0.05
HE index	13.31	8.78	3.56	<0.05	12.96	8.79	4.86	<0.05

p value: comparing Day 1 with Day 5 - 8 value

Table 3: Changes in HE index and HE grade

	Rifaximin + Lactulose	Lactulose	P value
Improvement in HE grades	31	24	0.325
HE index			
Improved	31	24	0.325
Unchanged	0	0	
Worsened	1	4	

DISCUSSION:

Rifaximin is an effective treatment for reversing HD. Several randomized controlled trials have found that rifaximin is at least as effective as current first-line therapy for improving HE levels at a dose of 400 mg tds. A meta-analysis by Karim M Eltawil, 17 published on World J Gastroenterol 2012,conducted a systematic review and meta-analysis of random effects of all eligible evidence identified by electronic and manual searches.7 studies that studied the efficacy of rifaximin (n = 184) against non-absorbable disaccharides (n = 165) revealed that both groups experienced a complete HE resolution or clinical improvement that primary researchers considered significant without achieving statistical significance (OR = 1.92, 95% CI: 0.79-4.68, P = 0:15). Bucci et al8 also showed the same efficacy as rifaximin and lactulose, with better tolerability and lack of side effects with rifaximin. Paik et al. 9 reported that both rifaximin and lactulose were effective in most patients (84.4% and 95.4% respectively) with a significant improvement in blood NH3, flutter tremor, mental state and psychometric tests. In a randomized study conducted by Sharma et al. 18 Comparison of rifaximin plus lactulose compared to lactulose alone in the treatment of manifest liver encephalopathy, 48 (76%) patients in the rifaximin group had more lactulose than 25 (44%) patients in the group who he only received lactulose. complete reversal of HE (P = 0.004) within 10 days. There was a significant reduction in mortality in the lactulose plus rifaximin group (15 (24%)) compared to lactulose alone.(28 (49.1%), P <0.05). In our study, the degree of mental state improved from 1.81 to 0.22 (p = <0.05) in the R + L group and from 1.57 to 0.43 (p = <0.05) in group L; using an independent paired t test (Table 2). But after applying the multivariate analysis of the variance test to compare the mental state score between two groups on days 1, 3, 5-8, we found that the difference in mental state improvement in the two groups was not statistically significant. ; 0.191). In our study, the degree of asterixis is improved by From 2.13 to 0.16 (p = <o.05) in the R + L group and from 2.18 to 0.39 (p = <0.05) in the L group after treatment. But after applying (Table 2) the multivariate analysis of the variance test to compare the degree of Asterixis between two groups on day 1, 3, 5-8, We found that the difference in the improvement of the degree of asterixis in the two groups was not statistically significant; (p = 0.465). In our study, after applying the independent t test, he demonstrated it; The degree of NCT improved from 3.84 to 1.75 (p = <0.05) in the R + L group and from 3.75 to 2.07 (p = <0.05) in the L group after treatment (Table 2). But after applying the multivariate analysis of the variance test to compare the degree of NCT between two groups on days 1, 3, 5-8, we found that the difference in the improvement of the degree of NCT in the two groups was not statistically significant; (p = 0.361) He demonstrated that both groups of drugs are equally effective in improving the degree of NCT after treatment. The combination of rifaximin + lactulose is not superior to lactulose alone to improve the degree of NCT in patients with hepatic

encephalopathy. In our study, after applying the independent t test, he demonstrated it; The serum ammonia content improved from 2 to 0.81 (p = <0.05) in the R + L group and 2.36 to 1.11 (p = <0.05) in group L after treatment (table 2). But after applying the multivariate variance analysis test to compare the grade of serum ammonia between two groups on days 1, 3, 5-8, we found that the difference in improving the grade of serum ammonia in the two groups were not statistically significant; (p = 0.417). After applying the multivariate analysis of the variance test to compare the HE index between two groups on days 1, 3, 5-8, we found that the difference in the improvement of the HE index in the two groups It was not statistically significant; (p = 0.523). In our study, the degree of hepatic encephalopathy improved in 31 out of 32, or 96.87% in the R + L group. In the lactulose group it improved in 24 out of 28 patients, that is, in 85.71%. After applying the exact Fisher test, he showed that there were no statistically significant differences in the improvement of HE grade in both groups after treatment. P-value (2 tails) 0.3251 Clinical efficacy was determined using the improvement of the HE index (Table 3).The combination of Rifaxim in + Lactulos e is effective in 31 out of 32, i.e. 96.87% and lactulose alone in 24 out of 28 patients, i.e. 85.71%, which is not statistically different, p = 0.3251 .Therefore, from the study we can conclude that the combination of rifaximin + lactulose is effective, but not superior to lactulose alone in the treatment of hepatic encephalopathy.

CONCLUSION:

The drug groups, combination of rifaximin + lactulose and lactulose are equally effective in the treatment of hepatic encephalopathy. But the combination of rifaximin + lactulose is not superior to lactulose to improve HE levels, the HE index, serum ammonia and the treatment of hepatic encephalopathy. Adverse effects included abdominal pain, diarrhea in a few patients. The limitations of the study are its non-randomized, small sample size study. Furthermore, such studies are needed in the future.

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