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Comparison of Rifaximin and Lactulose With Lactulose Alone in the Treatment of Acute Hepatic Encephalopathy in Patients With Liver Cirrhosis

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ABSTRACT

Hepatic encephalopathy (HE) is one of the common complications of liver cirrhosis. Lactulose is conventionally used for the treatment of hepatic encephalopathy. **Aims & methods:** The aim of this study was to evaluate the combined efficacy of lactulose plus rifaximin versus lactulose alone in the management of hepatic encephalopathy. 80 patients with HE were given lactulose alone and another 80 were given a combination of lactulose and rifaximin. They were monitored for 7 days for response *i.e.,* reversal of HE. **Results:** Initially 160 patients with HE, who met inclusion and exclusion criteria, were enrolled in this study (out of 183 screened). 80 patients were randomized in lactulose plus rifaximin group (group A) while the other 80 were placed in lactulose alone group (group B). Patients were given respective treatment and were monitored for improvement of HE by using West Haven (WH) criteria. Patients were assessed daily. Patients were monitored till recovery or death for 7 days, whichever occurred first. 62 (77.5%) patients in the rifaximin plus lactulose group showed reversal while 43(53.75%) patients in lactulose only group showed reversal of HE. Mortality was also less in the rifaximin plus lactulose group compared to lactulose alone group 17(21.25%) vs. 33 (41.25%) respectively ($P<0.05$). **Conclusion:** Rifaximin and lactulose have different mechanisms of action and act synergistically in combination and show better response in treating HE. This can result in significant decrease in morbidity and mortality.

Keywords: Liver cirrhosis, hepatic encephalopathy, rifaximin, lactulose.

INTRODUCTION

Cirrhosis is defined as the histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury, which leads to portal hypertension and end-stage liver disease[1]. Cirrhosis is the end result of liver damage caused by chronic liver disease. Common causes of chronic liver disease include hepatitis B and C and alcohol and fatty liver disease[2]. Cirrhosis is the twelfth leading cause of death by disease, accounting for 27,000 deaths each year in USA[3]. Hepatitis B is present in 4.3% and hepatitis C in 4.5-8% of general population of Pakistan[4-7].

Hepatic encephalopathy HE is defined as a metabolically induced, potentially reversible, functional disturbance of the brain and results as a complication of acute or chronic liver disease. It is most commonly associated with liver cirrhosis[8]. HE is graded into four grades by using West Haven Criteria (WH)[8,9]. The pathophysiology of encephalopathy is complex and multifactorial. Ammonia plays a key role in it[10]. It is a neurotoxin and impairs energy consumption of brain and halts nerve potential transmission through synapses. Ammonia is produced in digestive tract and converted into urea by liver through Krebs cycle, which is then excreted by kidneys. Cirrhotic liver is not able to convert ammonia into urea and its level increases in blood. It crosses blood brain barrier and causes encephalopathy.

Different Pharmacological agents are employed for the treatment of hepatic encephalopathy. Lactulose is the most commonly used treatment option. Different gut sterlising agents like metronidazole, vancomycin, oral neomycin and quinolones are also used. Rifaximin is used for prevention of recurrence of hepatic encephalopathy. It is a minimally absorbed non-aminoglycoside bacteriacidal antimicrobial agent with a broad spectrum in vitro and in vivo activity against gram-positive and gram-negative aerobic and anaerobic enteric bacteria. The role of rifaximin in acute hepatic encephalopathy is not studied sufficiently by large trials and needs probing. In one study, 76% patients given rifaximin plus Lactulose had reversal of HE compared with 50.8% taking Lactulose alone had complete reversal of HE. In the same study, there was also a significant decrease in mortality after treatment with lactulose plus rifaximin vs. lactulose and placebo (23.8% vs. 49.1%)[11]. In our study, we evaluated the efficacy and safety of rifaximin plus lactulose vs. lactulose alone for treatment of acute HE.

Objective

To determine the efficacy of combination of rifaximin plus lactulose in comparison with lactulose alone

PATIENTS AND METHODS

This was a prospective randomized controlled trial done in Gastroenterology department, Shaikh Zayed Hospital Lahore and study was conducted from October 2014 to March 2015.

Inclusion criteria

- All adult patients of both sexes aged 18 years and above
- Acute hepatic encephalopathy

Exclusion criteria

- Active alcohol intake <4 weeks before current episode
- Hepatocellular carcinoma
- Other metabolic encephalopathies
- Major psychiatric illness
- Significant comorbidity (such as advanced renal failure, heart disease, pulmonary disease etc.)

Diagnosis of cirrhosis was made on clinical basis involving laboratory parameters and ultrasound findings.

Hepatic encephalopathy

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West Haven criteria

West Haven criteria have four grades with each grade classified as follows:

- Grade I: Trivial lack of awareness Euphoria or anxiety Shortened attention span Impaired performance of addition
- Grade II: Lethargy or apathy Minimal disorientation for time or place Subtle personality change Inappropriate behavior Impaired performance of subtraction
- Grade III: Somnolence to semi-stupor, but responsive to verbal stimuli Confusion Gross disorientation
- Grade IV: Coma (unresponsive to verbal or noxious stimuli)[8-11]

Study Design

In this prospective randomized controlled trial, West Haven (WH) criteria was used to grade severity of HE[8-9]. Initially, precipitating factors like gastrointestinal bleeding, hypnotics use, and diuretics over dosage, spontaneous bacterial peritonitis or other septic conditions were identified and addressed. All relevant baseline investigations were sent. Baseline laboratory parameters included complete blood count, serum transaminases, serum urea and creatinine, serum electrolytes, international normalized ratio, serum ammonia, viral markers (for hepatitis B&C) if previously unknown, and abdominal ultrasound. Ascitic fluid analysis was done to rule in/out spontaneous bacterial peritonitis. After taking into consideration the inclusion and exclusion criteria, patients were randomized into two groups, A & B. Rifaximin, 550 mg twice a day

plus lactulose 30ml three times a day were given to patients in group A. Patients in group B were given only lactulose 30 ml three times a day. This treatment was given in addition to standard protocol for management of HE according to EASL guidelines[12]. Daily assessment of grade of HE was made using WH criteria. Treatment was given till complete recovery of PSE or patient discharge from hospital or death during the 7-day observation period. Recovery was identified as improvement of conscious level and reversal of cognitive functions by using WH criteria.

Same medication *i.e.*, rifaximin plus lactulose or lactulose alone was continued in both groups after recovery of hepatic encephalopathy for secondary prophylaxis. Child–Turcotte–Pugh (CTP) score was calculated using standard clinical and laboratory measures.

The end point of the study was complete reversal of HE as per WH criteria or death or 7 days time. Written informed consent was obtained from first-degree relative/attendant before induction in the study.

Statistical analysis

Eighty patients in each group were inducted in this time bound study. Data were expressed as mean ± S.D. For a comparison of categorical variables, χ^2 and Fisher's exact tests were used, and for continuous variables, Mann–Whitney test was used as appropriate. The probability level of $P<0.05$ was set for statistical significance. Statistical analysis was performed with SPSS software, version 20.

RESULTS

Screening of 183 patients with cirrhosis and HE was done. 23 patients were excluded from the study according to exclusion criteria. 160 patients fulfilling the inclusion and exclusion criteria (mean age 41±8.9years; male/female ratio 89:71) were enrolled in the study. Half of these patients (80) received rifaximin and lactulose (group A) while the other half (80) were given lactulose alone (group B) along with other standard treatment. Etiology of liver cirrhosis was hepatitis C in 139 (86.8%), hepatitis B in 7 (4.3%), alcohol in 3 (1.8%), and other causes in 11 (7.9%). One patient was in CTP class A (0.6%), 49 (30.6%) patients were in CTP class B and 110 (68.7%) were in CTP class C. Mean CTP score was 9.7±2.8. Distribution of patients according to CTP score class in both groups is described in Table 1. Of the patients, 3 (1.87%) had grade I HE, 29 (18.1%) had grade II, 51 (31.8%) had grade III, and 77(48.12%) had grade IV HE at the time of admission (Table 2). Baseline laboratory parameters were comparable in the both groups. Out of these 160 patients, 115 had an episode of HE in the past (60 group A patients and 55 group B patients). 62 (77.5%) patients in group A compared with 43 (53.75%) patients in group B had complete reversal of HE ($P<0.05$) within 7 days (Table 3). 17(21.25%) patients in group A while 33 (41.25%) in group B ($P<0.05$) died within 7 days (Table 3). HE was prolonged beyond 7 days in 1 patient in group A and 4 patients in group B.

Table 1: Patient distribution in the two groups according to severity of liver disease (as calculated by Child Turcotte Pugh Score).

	Group A (n=80)	Group B (n=80)
Number of patients in child class A	1	0
Number of patients in child class B	21	28
Number of patients in child class C	58	52

Table 2: Distribution of patients according to severity of HE (as per West Haven grading).

Grades	Number of patients
Grade I	3
Grade II	29
Grade III	51
Grade IV	77

Table 3: End results and on-treatment mortality of the two groups.

	Group A (n=80)	Group B (n=80)
Reversal of HE	62	43
Death	17	33

DISCUSSION

This study showed that combination of rifaximin plus lactulose is superior to lactulose alone in the treatment of HE. Rifaximin and lactulose have different mechanisms of action. Routinely, lactulose is employed as first line therapy for the treatment of HE even if its effectiveness in comparison with placebo has not been proven[13]. Lactulose is a non-absorbable disaccharide and acts as an osmotic laxative and also reduces colonic pH by employing gut flora. It reduces serum ammonia level by converting diffusible ammonia in colon to non-diffusible ammonium. Small intestinal bacterial overgrowth in cirrhotic patients is common and is associated with systemic endotoxemia[14] and is a significant predictor of development of minimal hepatic encephalopathy[15,16]. Rifaximin is a non-absorbable antibiotic acting in gut. Its plasma concentration is low and therefore minimal systemic adverse effects. It helps to restore gut microflora imbalance[17].

It was also shown that rifaximin plus lactulose was more beneficial for reverting acute episodes of HE (77.5% vs. 53.75%, $P<0.05$). Combination also decreases mortality (21.25% vs. 41.25%. $P<0.05$). Previous studies have shown that locally active antibiotics like neomycin are as effective as lactulose in the treatment of HE but have more systemic adverse effects[18,19]. Previous studies have compared rifaximin with lactitol[20] and rifaximin with lactulose[21,22] and have shown equal efficacy in the treatment of HE. In our study lactulose alone resulted in complete recovery of HE in 53.75% of patients as compared with 70-90% reported in previous published studies[16-18]. Sharma et al have shown similar results in their study[11]. Due to this diversity in mode of action of rifaximin and lactulose, both in combination act synergistically show better results in treatment of PSE than lactulose alone. The strength of this study is that more patients in advance stages of PSE (CTP class B 30.6% and CTP class C 68.7%) were studied. The limitation of the study was lack of serial ammonia level monitoring. Stool cultures should have been done that may have shown the effect of rifaximin on colonic bacteria.

Conflict of interest

None

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