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Research Article

**EFFECT OF USING LACTULOSE AND RIFAXIMIN IN  
COMPARISON WITH LACTULOSE ONLY THERAPY IN  
TREATMENT OF HEPATIC ENCEPHALOPATHY: A  
RANDOMIZED CONTROLLED TRIAL.**<sup>1</sup>Muneeba Akbar, <sup>2</sup>Moqadsa Jabeen, <sup>3</sup>Faiqua Nayyer, <sup>4</sup>Maryam, <sup>5</sup>Usama Sardar.<sup>1</sup>Postgraduate resident in department of internal medicine at POF Hospital, Wah Cantt, Pakistan.<sup>2</sup>WMO, THQ Pind Dadan Khan, Jhelum, Pakistan.<sup>3</sup>Medical Officer, BHU Rasul Mandi Bahu din, Pakistan.<sup>4</sup>MBBS, King Edward Medical University Lahore, Pakistan.<sup>5</sup>MD, Latin American School of Medicine, Havana, Cuba.**Abstract:**

**Objective:** To evaluate the effectiveness of using lactulose and rifaximin combination therapy for curing hepatic encephalopathy in adult patients and its comparison with lactulose only treatment.

**Method:** This research was conducted at Jinnah hospital Lahore, department of internal medicine during period of seven months, from December 2014 to June 2015 after taking consent from hospital ethical committee. The study design is randomised controlled trial. Sample size of one hundred and thirty patients was calculated by using WHO calculator. All these cases were stratified into two groups consisting of sixty five patients each. 30ml lactulose 8 hourly was given to one group and the other group was given lactulose and rifaximin 550mg 12 hourly for 10 days. Informed written consent was taken from patients' guardians. West-Haven Classification was used to determine grade two to four hepatic encephalopathy. Patients were followed up for 10 days after admission.

**Results:** The mean age of patients was 56.06±11.2 years amongst which females were 46.9% while males were 53.1%. 58.46% patients showed reversal by taking lactulose only therapy while 67.67% patients who were given lactulose and rifaximin treatment, after ten days of follow up. P value was 0.276, which was not statistically significant. The abovementioned results show that there was no difference in effectiveness of using lactulose and rifaximin combination treatment as compared to lactulose only treatment in patients with grade two to four hepatic encephalopathy.

**Key words:** Rifaximin, Lactulose, Hepatic encephalopathy, Chronic liver disease.

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**INTRODUCTION:**

Hepatic Encephalopathy is one of the fatal complications associated with liver disease. The defective hepatic function and portal-systemic shunting, lead to impaired detoxification of noxious substances of gastrointestinal origin which ultimately results in central nervous system symptoms [1]. The clinical features range from day-night reversal to cognitive impairments and coma. The risk factors associated with hepatic disease are chronic alcoholic ingestion, hepatitis B and C virus infection, previous histories of jaundice and certain drugs [2]. The various stages of hepatic encephalopathy range from mild confusion, drowsiness and cognitive impairments, stupor and coma [2,3]. The complicating factors are raised serum ammonia level, intestinal bleeding, constipation, alkalosis, hypokalemia, hypnotics and sedatives [4]. The reduction in serum ammonia level helps in treating hepatic encephalopathy.

The use of lactulose, a non-absorbable sugar has an effective role in short term management of hepatic encephalopathy, with minimal benefits on mortality reduction or long term disease management [5]. It is widely used in hepatic encephalopathy management worldwide because of low cost and easy availability. The major side effects associated with lactulose use include diarrhea and abdominal cramps [6].

[7] Rifaximin is based on rifamycin, it is an oral, non absorbable bactericidal agent effective against wide variety of bacterial species, which binds  $\beta$ -subunit of bacterial RNA polymerase and interferes with the transcription process. It eventually blocks the translocation step responsible for first phosphodiester bond formation. It is well tolerated and its use has been approved in treating hepatic encephalopathy in several countries [7,8] Multiple researches have been conducted to evaluate the therapeutic response associated with rifaximin use in hepatic encephalopathy, but there is much lack of research data availability in comparison with disease burden in Pakistani population. This research study aims in evaluating the efficacy of using rifaximin in addition to usual treatment of hepatic encephalopathy in patients of decompensated chronic liver disease (DCLD).

**METHODOLOGY:**

This research follows randomized controlled trial study pattern. One hundred and thirty patients who were presented to the department of internal medicine, Jinnah hospital Lahore were randomly selected after taking consent from hospital ethical

committee. The study duration was of seven months starting from December 2014 to June 2015. All patients were suffering from hepatic encephalopathy due to DCLD (decompensated chronic liver disease) i.e. they had abnormal liver texture on abdominal ultrasonography. Patients who had encephalopathy due to causes other than DCLD and those who showed any contraindication related to the tested drugs were excluded. Informed written consent was taken from patients' guardians. Sample selection was from patients admitted in department of internal medicine. West Haven classification was used to determine grade two to four hepatic encephalopathy. A questionnaire was designed and information like age, gender, residential address was collected. Lottery method was used to divide patients into two groups. Lactulose 30ml 8 hourly was given to first group, while rifaximin 550mg twelve hourly alongwith lactulose 30ml eight hourly was given to second group.

All patients were followed up for ten days and the treatment outcome in terms of recovery from disease was recorded on a performa. Rest of the usual treatment was given to all patients in accordance with hospital protocols.

Data was analysed by using SPSS version 20. For quantitative variables i.e. age and disease duration; mean, median and standard deviation from mean were calculated with inter-quartile range for variables, which were not normally distributed. For qualitative variables i.e. gender, hepatic encephalopathy grade and socio-economic status of patients, frequency and percentages were calculated. Control of effect modifiers and cofounders (age of patient, gender of patient, disease duration and hepatic encephalopathy grade) was achieved by stratification. Chi-square test was applied, p value of less than 0.05 was considered significant.

**RESULTS:**

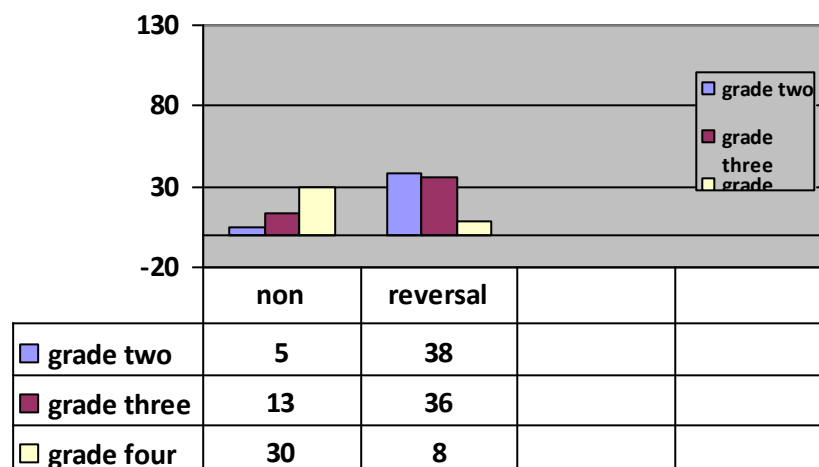
A hundred and thirty patients suffering from hepatic encephalopathy with DCLD as the cause and admitted in the internal medicine ward were considered part of the study. The mean age group of the patients was  $56.06 \pm 11.2$  years. 55.73 years was calculated as median age group with 14 as interquartile range. There were 61(46.9%) females while 69(53.1%) were males. If socio-economic status is considered, there were 18 patients from upper socioeconomic class, 48 patients were from middle class whereas 68 patients had lower socioeconomic status, which were 13.8%, 36.9% and 49.2% respectively.

In the beginning of research study, seventeen out of 65 patients in group A had grade II hepatic encephalopathy while 25 patients had grade III and 23 were suffering from grade IV hepatic encephalopathy. These were 26.15%, 38.46% and 35.38% respectively. In group A 38(58.46%) patients showed reversal.

There were 26 patients (40.0%) belonging to grade II, 24 patients were from grade III (36.92%), 15 patients

(23.07%) had grade IV hepatic encephalopathy in group B. Reversal was seen in 44 patients i.e. 67.69%, after 10 days of follow up. Stratification was done for age of patients i.e. p value 0.256, disease duration p value was 0.498, gender of patients p value was 0.579, socioeconomic status p value was 0.690, encephalopathy grade in the beginning of study p value was <0.01 and given treatment p=0.276.

Figure 1: Stratification for patient outcome in accordance with grade of hepatic encephalopathy in the beginning of research. (n=130)



### DISCUSSION:

Hepatic encephalopathy is a fatal complication of acute or chronic liver disease. The major contributing factor is raised serum ammonia level, which crosses blood brain barrier and impairs central nervous system function [2]. This complication of liver disease can be reversed by lowering serum ammonia level either by decreased absorption or by increased excretion from gut, which can be achieved with certain drugs or by diet modifications.

Lactulose is widely used worldwide to treat hepatic encephalopathy [9]. The common side effects associated with it are abdominal pain and diarrhea, electrolyte imbalance and dehydration, nausea and flatulence [6,8,9]. Several clinical trials have been done to estimate the use of antibiotics instead of lactulose in treating hepatic encephalopathy, for example neomycin, rifaximin and metronidazole etc. [13]

[7,10] Rifaximin is a derivative of rifamycin. It is a wide spectrum antibiotic and has poor oral absorption from gut thus stays in gut in active form and excreted through feces. It has minimal side effects as compared to other above-mentioned antimicrobials.

[12] Mactlayton DO, et al. have reported in their research that rifaximin has role in managing HE and to lower the disease remission as compared to lactulose, but results were statistically not significant. [11] Steven L Flamm, et al, mentioned in a study conducted in 2011 that rifaximin treatment has statistically significant benefits in lowering HE recurrence and its treatment as compared to placebo.

Hepatic encephalopathy is one of the common complications in patients with DCLD in Pakistan, but unfortunately less research data is available regarding management of HE in Pakistani population. This research study aims in evaluating the effect of using rifaximin in combination with lactulose instead of

using lactulose only treatment to manage HE patients. The current study shows that there is no statistically significant role of rifaximin and lactulose in comparison with lactulose only treatment in HE patients. The authors suggest conducting more clinical trials on a larger scale. PSE index (portal systemic encephalopathy index) has been widely used to evaluate mental status, it was devised by Conn HO et al. However, this system use has been strongly objected by FDA. Thus, authors recommend using new mental status evaluation system which meets FDA's requirement criteria and aids in studying effect of rifaximin in treatment of hepatic encephalopathy.

### CONCLUSION:

The current research study shows no effect of rifaximin and lactulose combination treatment in managing hepatic encephalopathy instead of lactulose only treatment.

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