CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.1461052

Available online at: http://www.iajps.com Research Article

RCT RESEATCH STUDY FOR CURING HEPATIC ENCEPHALOPATHY AND ITS COMPARISON WITH LACTULOSE ONLY TREATMENT, THE EVALUATION OF USEFULNESS, FOR TREATMENT OF HEPATIC ENCEPHALOPATHY

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Abstract:
Objective: *Research was held for the evaluation of usefulness, for treatment of hepatic encephalopathy by means of lactulose and rifaximin combination therapy and its comparison with lactulose only treatment in adult patients.*
Study Design: *Randomized Controlled Trial (RCT).*
Place and Duration of Study: *Current research study was held for the period of 7 months from October, 2017 to April, 2018 at Services Hospital, Lahore.*
Method: *With the help of WHO calculator 130 patients were selected for the research purpose. Equally divided the patients into two groups as the strength of each group was 65. One group was medicated with 550mg of lactulose and rifaximin twice in a day and the second group was given 30ml of lactulose three times in a day for the duration of ten days. From patients and their guardians took an informed written consent. Definition of grade two to four hepatic encephalopathy was done through West-Haven Classification method. After starting the treatment patients were observed for ten days.*
Results: *Amongst the selected patients 53.08% were men and 46.92% were women with average age of 55.95 ± 10 years. After observation of ten days, 67.68% patients were found with positive recovery who were medicated with rifaximin and lactulose. On the other hand, the patients who were treated with lactulose only resulted 58.45% recovery. Resulted P-value was 0.276 that was totally not significant statistically.*
Conclusion: *Our research concludes that no prescribable difference was found in effectiveness of treatment with lactulose and rifaximin combination as compared to lactulose only medical treatment in patients with grade two to four hepatic encephalopathy.*
Key words: *Chronic liver disease (CLD), Hepatic encephalopathy, Lactulose, Rifaximin.*

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Please cite this article in press Shaneela Sattar et al., ***RCT Reseatch Study for Curing Hepatic Encephalopathy and Its Comparison with Lactulose Only Treatment, the Evaluation of Usefulness, For Treatment of Hepatic Encephalopathy .,*** *Indo Am. J. P. Sci, 2018; 05(10).*

INTRODUCTION:

Amongst the various one of the disastrous Complexity related with liver disease is hepatic encephalopathy. portal-systemic shunting and The defective hepatic function, results in poor diagnosis of toxic substances that will finally produce the symptoms of central nervous system. The medical features range from sleep-wake inversion to coma and cognitive impairments. The risk factors related with hepatic infection are previous histories of jaundice and certain medication, chronic alcoholic ingestion, HCV and HBV infection. Side effects of various stages of hepatic encephalopathy coma, mild confusion, stupor cognitive impairments and drowsiness. The complex issues are hypnotics, sedatives hypokalemia, alkalosis, constipation, intestinal bleeding and raised serum ammonia level. The reduced level of serum ammonia supports in curing hepatic encephalopathy.

Although use of lactulose is a long term disease management but it is commonly advised for hepatic encephalopathy treatment for the reason that it is easily available and cheap in cost. Abdominal cramps and diarrhea are the main negative effects related with the use of lactulose.

Rifamycin is the basics of rifaximin, it is non absorbable oral bactericidal agent. That's why it is effective against comprehensive range of bacterial classes, which interferes with the transcription process and binds **β**-subunit of bacterial RNA polymerase. It ultimately deters the translocation step which is responsible for first phosphodiester bond formation. In many countries its use for treatment of hepatic encephalopathy has been permitted. Response of rifaximin when used for hepatic encephalopathy has been analyzed through many other research studies but still there is very less information about the disease is available in Pakistan. Current research study was held for the evaluation of usefulness in treatment of hepatic encephalopathy in patients of decompensated chronic liver disease (DCLD) with lactulose mixed by rifaximin.

METHODOLOGY:

This research was based on randomized controlled trial study design. Total numbers of 130 randomly selected patients were chosen for current study after having the written permission of ethical committee of services hospital, Lahore. Current research study was completed in the period of seven months staring from October, 2017 to April, 2018. Due to DCLD (decompensated chronic liver disease) all patients were suffering from hepatic encephalopathy as symptoms was abnormal liver texture on abdominal ultrasonography. Those patients were not included in the study who showed any contraindication related to the tested drugs or suffering from encephalopathy due to reasons other than DCLD. Determined the grade 2 to 4 hepatic encephalopathy by the help of West Haven classification. Collected data about residential address, age, gender. Equally divided the patients into 2 sections. One section was medicated with 550mg of lactulose and rifaximin twice in a day and the second section was dosed with 30ml of lactulose three times in a day for the duration of ten days. Results were calculated after 10 days observation on the bases of recovery from the disease and record was maintained on a paper.

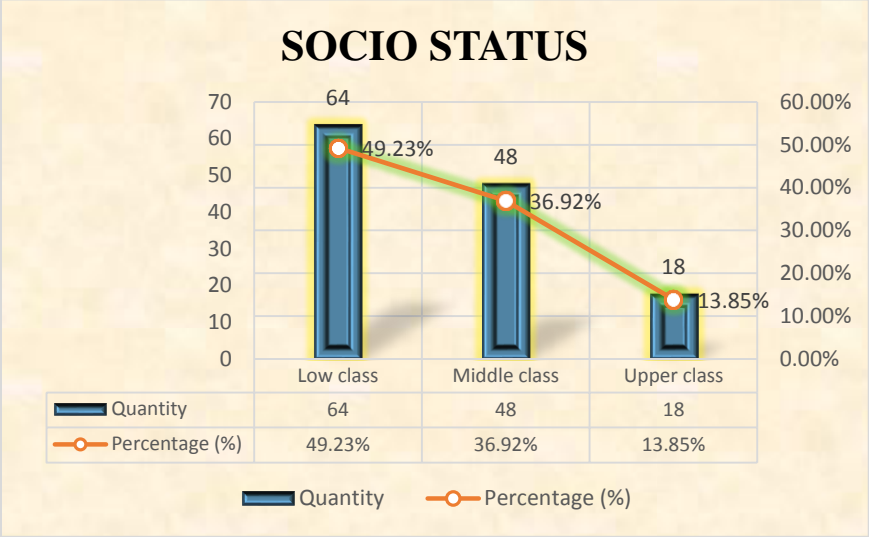
An analysis of collected data was carried out by using SPSS software version 25. Age of the patients and duration of the disease was selected as mean quantitative variables and with inter quartile range for variables calculated the standard deviation, normally which were not divided. Percentage and Frequency was calculated through qualitative variables such as socio-economic status of patients, gender and hepatic encephalopathy grade. Stratification was used to achieve the control of co-founders and modifiers. Applied the chi-square test, calculated P-value was <0.05 which was considered significant.

RESULTS:

Patients for the study were selected from those who were admitted in the medical ward of the hospital and facing hepatic encephalopathy due to DCLD in total number of 130 with average age of 55.95 ± 10 years from which 53.08% (69) were men and 46.92% (61) were women. Keeping in view of socio economic status of these patients, there were 49.23% (64) patients having lower socioeconomic class, 13.85% (18) patients from upper socioeconomic status and 36.92% (48) patients were from middle class. Details are presented in the table below.

Table No1: Classification According to Socio Economic Status

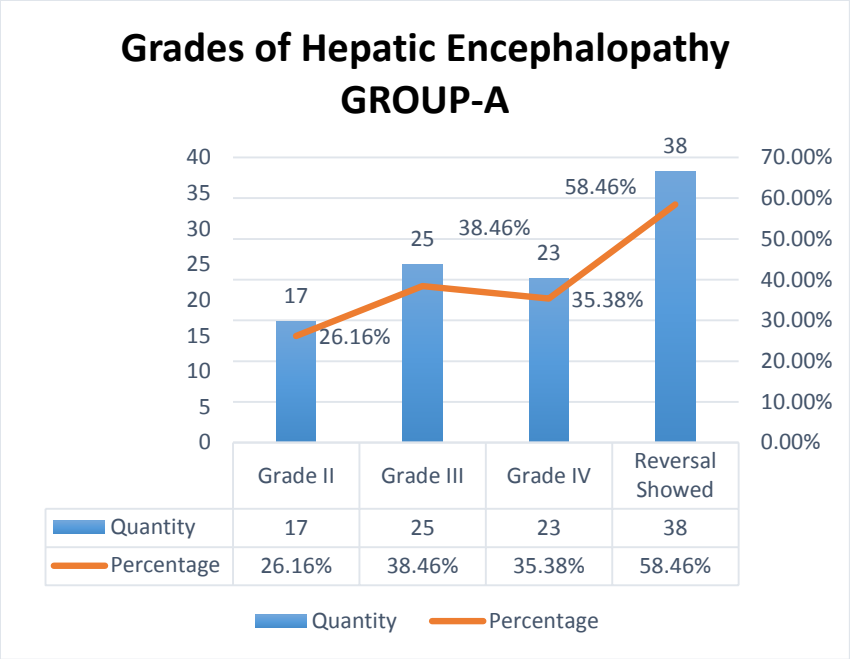
socio economic status	Quantity	Percentage (%)
Low class	64	49.23 %
Middle class	48	36.92 %
Upper class	18	13.85 %



Patients were divided into 2 groups as group A and group B. Out of 130 patients each group was having 65 members. In group A there was 35.38% (23) patients in grade IV hepatic encephalopathy, 38.46% (25) patients in grade III hepatic encephalopathy and 26.16% (17) patients in grade II hepatic encephalopathy. From this group reversal was showed by 58.46% (38) patients. Details are given in table below.

Table No2: Classification According to Grades of Hepatic Encephalopathy Group-A

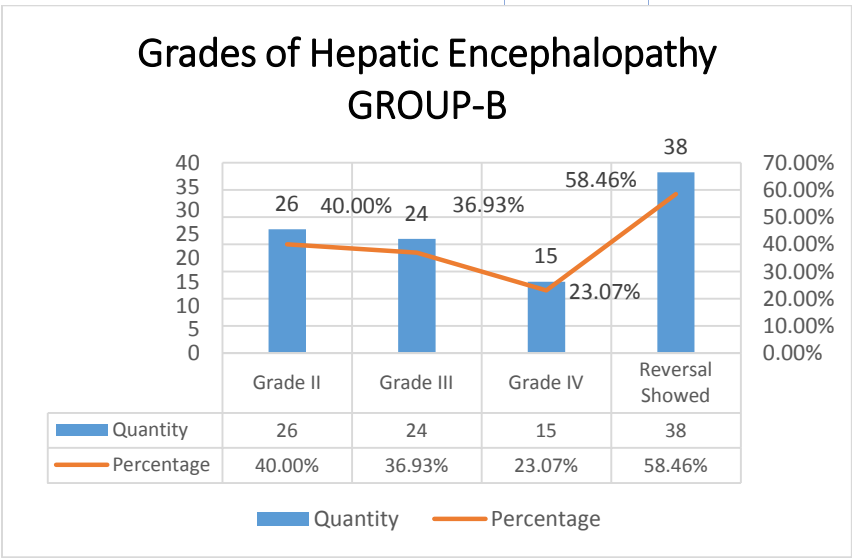
Grades of Hepatic Encephalopathy	Quantity	Percentage
Grade II	17	26.16 %
Grade III	25	38.46 %
Grade IV	23	35.38 %
Reversal Showed	38	58.46 %



In group B there was 36.93% (24) patients in grade III hepatic encephalopathy, 23.07% (15) patients in grade IV hepatic encephalopathy and 40.00% (26) patients in grade II hepatic encephalopathy. From this group reversal was showed by 67.69% (44) patients. Details are given in table below.

Table No2: Classification According to Grades of Hepatic Encephalopathy Group-B

Grades of Hepatic Encephalopathy	Quantity	Percentage
Grade II	26	40.00%
Grade III	24	36.93 %
Grade IV	15	23.07 %
Reversal Showed	38	58.46 %



Stratification was carried out for age of patients i.e. given treatment P = 0.276, socioeconomic status P value was 0.690, encephalopathy grade in the beginning of study P value was <0.01, P value 0.256, patients gender P value was 0.579and disease duration P value was 0.498.

DISCUSSION:

The exact reason of hepatic encephalopathy is unidentified. However, it is commonly activated by a buildup of toxins in the blood. This happens when liver fails to break down toxins properly which might be due to chronic or acute liver infection. These toxins will raise the serum ammonia level which crosses blood brain and harms the function of central nervous system. This problem of liver infection can be overturned by decreasing serum ammonia level either by augmented excretion from chitterlings or by reduced absorption, which can be managed by diet adjustments or with precise medications.

Treatment of hepatic encephalopathy is mostly carried out by using lactulose. Commonly known negative reactions related to lactulose are flatulence, nausea, dehydration, electrolyte imbalance, diarrhea and abdominal pain. Many researches were conducted to evaluate the use of antibiotics such as metronidazole, neomycin and rifaximin as an alternative of lactulose for the treatment of hepatic encephalopathy. Rifaximin is an inferential of rifamycin. It has less oral absorption from gut so it remains in chitterlings as an active agent and egested through stool. Compared to other antibiotic, Rifaximin have miner reactions or side effects. In a research study by Mactlayton DO, et al it was found that for treatment of hepatic encephalopathy rifaximin has effective role to decrease the remission of it than lactulose, but consequences were not significant statistically. According to another study by Steven L Flamm, et al, it was found that rifaximin treatment as compared to placebo medication has significant results in reducing the reappearance of hepatic encephalopathy.

In Pakistan the general complexity in patients infected by DCLD is HE, and unluckily poor information is available for the treatment of hepatic encephalopathy. The purpose of this study was to find out the effectiveness of rifaximin treatment combined with lactulose beside only lactulose treatment to cure HE infected patients. According to resultant data there is no significant effect of lactulose and rifaximin as compared to lactulose only treatment in patients of HE. Evaluation of the mental status was done through portal systemic encephalopathy index (PSE) as it was recommended by Conn HO et al. but FDA greatly opposed the use of PSE index. Therefore, for studying effects of rifaximin in treatment of hepatic encephalopathy it is strongly suggested to use such a mental status evaluation system that could meet the criteria of FDA standers. More research studies are recommended to be held to evaluate the rifaximin efficiency.

CONCLUSION:

According to resultant statistics of the current study it was found that there is no significant effect of lactulose and rifaximin combined medication as compared to lactulose only treatment in patients of HE. It is suggested to carry out more research studies in Pakistan to examine the results of rifaximin and lactulose combination.

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