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Efficacy of Lactulose Vs Lactulose with Rifaxamin in patients with Hepatic Encephalopathy: A Randomized Control Trial

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Abstract:

Introduction: Hepatic encephalopathy (HE) is one of the deadliest complications of cirrhosis. The basic underlying pathophysiology is the increased production of ammonia which can cross the blood brain barrier and can influence in multiple ways. For managing HE various therapeutic regime have been tried in the past with varying degree of success grate and side effect profiles. Neomycin, Enema, Lactulose, Metronidazole, Vancomycin, Rifaxamin etc. are the various modalities used. Lactulose is the most widely used and Rifaxamin; an antibiotic is recently used with good success rate.

Objective: To compare the outcome of lactulose alone versus lactulose with Rifaxamin in cases with hepatic encephalopathy.

Methodology: A randomized control trial was conducted on indoor patients of medical departments, Mayo Hospital. Lahore from June 2017 to December 2017. The cases of hepatic encephalopathy of any grade within last 7 days of its onset with age range of 20-60 years were included. The cases with end stage cardiac or renal failure were excluded. The cases were divided into two groups; A and B. The group A was treated with lactulose alone in a dose to 20 to 100 ml per day to maintain stool frequency of at least 2 per day and the group B was treated with same amount of lactulose along with Rifaxamin in a dose of 550 mg thrice a day. The efficacy was assessed daily till there were no signs and symptoms of hepatic encephalopathy till day 7 where final outcome was seen to label efficacy or mortality as Yes or No.

Results: In the present study, 100 cases of hepatic encephalopathy were included. Out of these 50 were in each group. The maximum cases were in Child Pugh class in both groups comprising 26 (52%) and 25 (50%) in group A and B respectively. The mean age at presentation was 46.73± 9.13 years in A as compared to 51.25± 9.04 years in group B with p= 0.54. The efficacy in group A was seen in 28 (56%) of cases and in group B as 38 (76%) of cases with p= 0.01. This difference was also statistically significant in terms of mortality which was seen I n 22 (44%) of cases in group A and 12 (24%) in group B (p=0.01).

Conclusion: Combination of lactulose plus Rifaxamin is significantly better as compared to lactulose alone for the treatment as well as to reduce mortality in cases of hepatic encephalopathy.

Key words: Lactulose, Rifaxamin**,** Cirrhosis, Encephalopathy

Introduction:

Liver cirrhosis is one of the salient diseases, which are encountered in the medical wards and is one of the leading cause of health care burden. It is defined as a chronic inflammation and ongoing liver damage that results in liver fibrosis and scarring; an irreversible process. There are multiple etiologies that can lead to its development and are variable globally depending upon the risk factors and epidemiological variance. Hepatitis B and C are the commonest causes in the developing world while alcoholism is the most common in developed world followed by hepatitis C virus infection. The other factors involved are drugs, toxins and storage disorders like Wilson disease, hemochromatosis etc.[1-2] Cirrhosis can lead to various physiological as well as structural impairments and can end up in different complications. These include decreased albumin synthesis, prolonged prothrombin time, increased liver enzymes and clinical complications like upper gastrointestinal bleed due to portal hypertension, ascites, hepatic encephalopathy, hepatorenal syndrome etc.[3-4]

Hepatic encephalopathy is one of the deadliest complications as it can predispose to various complications like aspiration pneumonia which can be fatal. The basic underlying pathophysiology is the increased production of ammonia which can cross the blood brain barrier and can influence in multiple ways.[5-6]Altered sleep is one of the first sign of hepatic encephalopathy and is defined as grade I on West Haven Criteria and on the other hand overt coma is labeled as grade IV. The other clinical symptoms include flapping tremor, hyperreflexia, irritability, drowsiness and decerebrate posturing with or without altered mental status and irrelevant talks.[7-8]

Multiple therapeutic options have been tried in the past with varying degree of success rate and side effect profiles. Neomycin, Enema, Lactulose, Metronidazole, Vancomycin, Rifaxamin etc. are the various modalities used. Lactulose is the most widely used and Rifaxamin; an antibiotic is recently used with good success rate.[9-12]

Objective:

To compare the outcome of lactulose alone versus lactulose with Rifaxamin in cases with hepatic encephalopathy.

Methodology:

This randomized control trial was carried out at Mayo Hospital, Lahore during June 2017 to December 2017. The cases of hepatic encephalopathy of any grade within last 7 days of its onset with age range of 20-60 years were included. The cases with end stage cardiac and renal failure were excluded. The diagnosis of liver cirrhosis was made by shrunken liver size on ultrasonography abdomen, increased spleen size with or without ascites and other clinical features like palmar erythema, Dupuytren's contracture and caput medusa. The cases were divided into two groups labelled as A and B by simple lottery method containing 50 cases in each. The group A was treated with lactulose alone in a dose to 20 to 100 ml per day to maintain stool frequency of at least 2 per day and the group B was treated with same amount of lactulose along with Rifaxamin in a dose of 550 mg thrice a day. The efficacy was assessed daily till there were no signs and symptoms of hepatic encephalopathy. At day 7 final outcome was assessed to label efficacy or mortality as yes or no. All the results were recorded on a proforma. The data was processed by using SPSS version 23.0. The qualitative variables were

presented in terms of frequency and percentages. For quantitative data mean and standard deviation were used. The data was 4compared using independent sample t test and chi square test taking p value of ≤ 0.05as significant.

Results:

In the present study, 100 cases of hepatic encephalopathy were included, 50 in each group. The maximum cases were in Child Pugh class in both groups comprising 26 (52%) and 25 (50%) in group A and B respectively (table I).

Table I. Stratification of cases with respect to Child Pugh class

Child Pugh class	Group A (n= 50)	Group B (n= 50)	
A	4 (8%)	3 (6%)	p= 0.78
B	20 40%)	22 (44%)	
C	26 (52%)	25 (50%)	

The mean age at presentation was 46.73 ±9.13years in group A as compared to 51.25 ±9.04 years in group B with p= 0.54 as shown in table II.

Table II. Study variables

Variables	Group A (n= 50)	Group B (n= 50)	p value
Age	46.73± 9.13	51.25± 9.04	0.54
Weight	67.21± 11.73	71.03± 12.45	0.38
Duration of cirrhosis	7.12± 3.28	6.36± 4.09	0.79

There was no significant difference in terms of grade of hepatic encephalopathy in both groups with p value of 0.31 as in table III.

Table III. Stage of Encephalopathy

Encephalopathy Grade	Group		p value
	A	B	
I	2 (4%)	2 (4%)	p= 0.31
II	6 (12%)	4 (8%)	
III	22 (44%)	19 (38%)	
IV	20 (40%)	25 (50%)	

The efficacy in group A was seen in 28 (56%) of cases a nd in group B as 38 (76%) of cases with p= 0.01. This difference was also statistically significant in terms of mortality which was seen in 22 (44%) of cases in group A and 12 (24%) in group B (p=0.01) as in table IV.

Table IV. Trial Groups outcome with regards to efficiency and mortality

Variable	Group A (n= 50)	Group B (n= 50)	p value
Efficacy	28 (56%)	38 (76%)	0.01
Mortality	22 (44%)	12 (24%)	0.01

Discussion:

The number of cases affected by hepatitis B and C are rising day by day in the 3rd world countries due to poor hygienic conditions and lesser priority in the health providing departments; hence the cases with ongoing damage and overt cirrhosis are increasing. Hepatic encephalopathy is one of the unwanted late onset complications that can induce a coma and serve as a source to an inciting event leading to death ultimately. There is always a need for a good drug with, better efficacy and minimal side effects to cope with this complication.

The efficacy in group A was seen in 28 (56%) of cases and in group B as 38 (76%) of cases with p= 0.01. The findings of our study were supported by published data that also revealed that the combination of lactulose and Rifaxamin was better as compared to lactulose alone.[13-15] Palik et al also conducted the study on same agents and revealed significant better results with combination therapy having p value less than 0.05.[13] This can be explained by the factor that both of these drugs are used for the treatment of acute hepatic encephalopathy and hence combining both of these drugs led to better outcome as compared to single drug use. The lactulose basically acts as stool softener and avoids stasis of protein in gut and then conversion of protein into ammonia; while Rifaxamin acts by alteration in the normal flora of the gut towards a better balance.[16-17]However as compared to placebo; lactulose in the past has shown significant better efficacy in cases of hepatic encephalopathy, but not as good as was seen in combination therapy in present study.[18]

This difference was also statistically significant in terms of mortality which was seen in 22 (44%) of cases in group A and 12 (24%) in group B (p=0.01). This finding was also identical to a national study where they also found statistically significant difference in both groups and as compared to 17l cases in combination therapy, 33 cases died in cases treated with lactulose alone out of 80 cases with p < 0.05.[19]The reason of this can be explained by the fact that the cases that had better efficacy came out of this complication earlier and those with persistent encephalopathy developed some complication and led to higher mortality.

Conclusion:

Combination of lactulose plus Rifaxamin is significantly better as compared to lactulose alone for the treatment as well as mortality benefit in cases of hepatic encephalopathy.

Conflict of Interest:

All authors declare no conflict of interest.

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