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Research Article

**TO COMPARE THE EFFICACY OF LACTULOSE ALONE AND
LACTULOSE WITH RIFAXAMIN IN PATIENTS WITH
HEPATIC ENCEPHALOPATHY**¹Ahmad Zahid, ²Muhammad Akash, ³Zauraiz Anjum

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Abstract:

Objective; To compare the efficacy of lactulose alone and in combination with rifaxamin in cases with hepatic encephalopathy.

Patients and methods It was a randomized control trail conducted at Al-Nafees Medical college, Islamabad & Sir Ganga Ram Hospital, Lahore during July to December 2018. In this study total 120 cases of liver cirrhosis were identified their encephalopathy was grades according to West Haven's criteria. The cases with hepatocellular carcinoma, active alcoholics, psychiatric patients and those with encephalopathies due to any other cause and with renal failure were excluded. The cases were then divided into two equal groups with 60 cases in each group. The group A was treated with lactulose alone and B with lactulose plus rifaxamin in their standard doses. The cases were then followed and assessed for their improvement in symptoms and assessed on West Haven's scale and the cases with complete resolution of symptoms were labeled as cured. The mortality benefit was also noted.

Results; In this study there were 120 cases out of which 91 had hepatitis C, 20 had hepatitis B while 9 had both B & C. The mean age was 43.24 ± 8.34 years and mean duration of symptoms was 3.45 ± 0.8 days. There were 60 cases in each group. Group A had 29 (48.33%) males and 31 (51.67%) females while Group B had 34 (48.33%) males and 26 (51.67%) females. There was no significant difference in terms of child pugh class in both groups with $p = 0.69$. There was also no significant difference in both groups in terms of grades of encephalopathy ($p = 0.21$). However there was significant better efficacy and decreased mortality in group B as compared to A with p values of 0.02 and 0.03 respectively.

Conclusion; Hepatic encephalopathy is a fatal complication. Lactulose combined with rifaxamin has significant improvement in encephalopathy as well as in reducing mortality.

Key words: Hepatic encephalopathy, lactulose, rifaxamin.

Corresponding author:

Ahmad Zahid,

QR code



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INTRODUCTION:

Cirrhosis is described as end stage disease resulting due to progressive liver damage. This can be due to various etiologies comprising hepatitis (due to various viruses), alcohol, drugs, toxins, hereditary disorders etc. This end up in architectural distortion and due to fibrosis and damage, it interferes with the normal liver functioning. This is an irreversible process and the ultimate recovery can be achieved by transplantation only. Patients present with wide range of symptoms depending upon the type of complication developed in each case including ascities, GI bleeding, hepato-renal syndrome, encephalopathy etc. Cirrhosis had led to more 25 thousand deaths in US in a single year in 2000. Hepatic encephalopathy is a well reported and dreadful complication of cirrhosis. [1-2]

There are multiple theories regarding its development. The most popular is the ammonia theory which describes that there is increased production of ammonia in such cases by gut flora that surpasses the detoxification capabilities of the liver and cross the blood brain barrier and affect the brain in multiple ways. Secondly there is another theory regarding imbalance between the ratios of plasma aromatase amino acid to branched chain amino acids. This leads to more of the aromatase amino acid resulting more of such neurotransmitters that can interfere with normal functioning. The other one is GABA receptor inhibition at the post synaptic membrane. [3-6]

Patients can present with variety of symptoms, among which the diurnal sleep variation is the primary pattern. Later on asterixia (flapping tremors over outstretched hands), bradykinesia, hyper reflexia on deep tendon reflex and transient de-cerebrate posturing, alerted mental status and irrelevant talks, fits, coma and focal neurological deficits are the other complications to develop. [7-8]

A number of treatments have been tried either singly or in combination of two or more and in comparison with placebos as well. These included lactulose, lactitol, anemas, dietary restriction of dietary protein and oral antibiotics in the form of flagyl, neomycin, vancomycin, rifaxamin, probiotics, amino acids and multiple minerals have been tried. They have shown different degree of effectiveness. However flagyl, lactulose and enema are the most commonly used. Rifaxamin is an oral antibiotic which is not absorbed in the gut and has shown good efficacies in altering gut flora. [9-12]

PATIENTS AND METHODS:

It was a randomized control trial conducted at Al-Nafees Medical college, Islamabad & Sir Ganga Ram Hospital, Lahore during July to December 2018. In this study total 120 cases of liver cirrhosis were identified and selected. Liver cirrhosis was confirmed by signs and symptoms and on USG abdomen with shrunken size and dilated portal vein with splenomegaly. The encephalopathy was grades according to West Haven's criteria. The cases with hepatocellular carcinoma, active alcoholics, psychiatric patients and those with encephalopathies due to any other cause and with renal failure were excluded. These cases were then admitted and their all baseline investigations were sent including complete blood examination, hepatitis B and C serology, liver function tests, PT, APTT and renal function tests. The cases fulfilling the inclusion criteria were then divided into two equal groups with 60 cases in each group via shield opaque method. Then group A was treated with lactulose alone and group B was with lactulose plus rifaxamin in their standard doses. The cases were then followed and assessed for their improvement in symptoms and assessed on West Haven scale and the cases with complete resolution of symptoms were labeled as cured. The mortality benefit was also noted.

West Haven criteria:

The cases with hepatic encephalopathy were divided into following four groups according to these criteria;

- **Grade 1;** Trivial lack of awareness; euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction
- **Grade 2;** Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behavior
- **Grade 3;** Somnolence to semi-stupor, but responsive to verbal stimuli; confusion; gross disorientation
- **Grade 4;** Coma

STATISTICAL ANALYSIS:

A sample of 60 cases in each group was selected. The data was entered and analyzed on SPSS version 20.0. The categorical data was checked for frequencies and percentages. For continuous data, independent sample t test and for categorical data chi square test was used to compare the two groups. Both groups were also compared for efficacy and mortality benefit. Post stratification chi square test was applied and p value of ≤ 0.05 was considered as significant.

RESULTS:

In this study there were 120 cases out of which 91 had hepatitis C, 20 had hepatitis B while 9 had both B & C. The mean age was 43.24 ± 8.34 years and mean duration of symptoms was 3.45 ± 0.8 days. There were 60 cases in each group. Group A had 29 (48.33%) males and 31 (51.67%) females while Group B had 34 (48.33%) males and 26 (51.67%) females. There was no significant difference in terms

of child pugh class in both groups with maximum cases was in Class C in both groups with $p = 0.69$ (table 1). There was also no significant difference in both groups in terms of grades of encephalopathy ($p = 0.21$) as shown in table 2. However there was significant better efficacy and decreased mortality in group B as compared to A with p values of 0.02 and 0.03 respectively (table 3).

Table 1. Distribution of patients according to child pugh class

Child pugh class	Group A (n= 60)	Group B (n= 60)	p= 0.69
A	2 (3.33%)	1 (1.67%)	
B	19 (31.67%)	22 (36.67%)	
C	39 (65%)	37 (61.67%)	

Table 2. Encephalopathy grading between two groups

Grade	Treatment group		p value
	Group A	Group B	
I	4 (6.67%)	3 (5%)	p= 0.21
II	8 (13.33%)	6 (10%)	
III	20 (33.33%)	18 (30%)	
IV	28 (46.67%)	33 (55%)	

Table 3. Efficacy and mortality comparison.

Variable	Group A (n= 60)	Group B (n= 60)	p value
Efficacy	31 (51.67%)	42 (70%)	0.02
Death	29 (48.33%)	18 (30%)	0.03

DISCUSSION:

Liver cirrhosis especially due to hepatitis B and C is a great health concern and their number is on the rise in developing countries where there are lesser health facilities and poor awareness. This leads to progression of disease and then complications like hepatic encephalopathy have been observed which if not managed aggressively can be fatal. A number of pharmacological and non pharmacological maneuvers have been considered to avoid this with different degree of success.

In this study the efficacy with lactulose alone was seen in 31 (51.67%) cases as compared to higher success with the combination of lactulose and rifaximin affecting 42 (70%) of cases with significant p value of 0.02. This was also observed by many other studies as well that found this

combination as more effective. [13-15] In a study done by Palik YH et al significant improvement was seen in cases with combined therapy. [13] The reason for higher success of combined therapy as compared to alone can be due to additive effects of these drugs. Lactulose is a polysaccharide which is non absorbable and it works as an osmotic laxative and it also interferes with the action of the gut flora and resulting in alteration of the pH in the gut. It also enhances the cleared of ammonia from the gut by converting it from diffuse able form to non diffusible ammonium form. On the other hand rifaximin is an antibiotic which is not absorbed through the gut and it helps creating the balance between the gut flora. [16-17] While in another study done by Als-Nielsen B et al, the lactulose was compared with placebo and there was even no significant difference was seen as well. [18]

The mortality was also better reduced by the combination therapy as compared to alone where it was seen in 29 (48.33%) cases with lactulose only and 18 (30%) cases with combination therapy with significant difference of 0.03. Similar was observed by other studies. [14,19-20] According to a study by Irimia R et al the rifaximin only too was superior to lactulose in encephalopathy. [19] A study done by Haq MIU et al also revealed significant improvement in mortality where out of their both groups of 80 patients 33 died with lactulose alone as compared to 17 only with combination therapy. [20] This also can be explained the same pathophysiology and mechanism of action of the drugs. The cases with better and early clearance of the gut also had lesser ammonia to cause encephalopathy and the other causes like aspiration pneumonia, nutritional deficiencies and other complications like bed sore sepsis etc has also lesser chances to develop and that's why the mortality benefit was higher.

There were few limitations of this study as the data was collected only for complete resolution and not for betterment in grade of encephalopathy and neither was assessed for duration taken to cure.

CONCLUSION:

Hepatic encephalopathy is a fatal complication. Lactulose combined with rifaximin has significant improvement in encephalopathy as well as in reducing mortality.

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