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Research Article

Comparative efficacy of rifaxamin vs metronidazole in the treatment of hepatic encephalopathy grade 3 & 4

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ABSTRACT

Objectives: To compare efficacy of rifaxamin and metronidazole for the treatment of hepatic encephalopathy grade 3, 4.

Material and methods: This comparative study was conducted at Department of Medicine DHQ Teaching Hospital, Sargodha from March 2017 to September 2017 over the period of 6 months. Total 120 cases of HE grade 3 & 4 were selected. Two equal groups A & B were made. Group A was managed with rifaximin and Group B was managed with metronidazole. Efficacy of both drugs was compared.

Results: Total 120 patients (60 patients in each group) with HE were selected for this study. Mean age of the patients was 49.43 ± 6.866 years, mean age in group A was 49.37 ± 6.757 years and mean age in group B was 49.50 ± 7.029 years.

Out of 60 patients of group A, efficacy of treatment was noted in 14 (23.33%) patients and out of 60 patients of group B, treatment was found effective in 45 (75%) patients. Significantly higher rate of efficacy was noted in patients of group A as compared to group B with p value 0.000.

Conclusion: In this study efficacy of treatment was significantly higher in patients managed with Metronidazole as compared to patients managed with Rifaxamin. Statistically significant association of efficacy with age and gender are noted.

Key words: Hepatic encephalopathy; Lactulose; Neomycin; Non-absorbable disaccharides; Rifaximin

INTRODUCTION

Hepatic encephalopathy describes a wide spectrum of often-reversible neuropsychiatric abnormalities that occur in patients with acute or chronic liver disease.[1-2]Often, the term "portal-systemic encephalopathy" is used to emphasize the failure of the liver to detoxify toxins that escape from the intestine. These toxins thus bypass the liver and enter the systemic circulation, causing the primary or secondary changes in brain neurochemistry that produce symptoms of hepatic encephalopathy. This metabolic disorder is characterized by reversibility, which suggests a lack of persistent structural lesions in the brain.[3]

Hepatic encephalopathy can be develop due to many factors which include gastro-intestinal bleeding, infections, constipation, electrolyte imbalance (hyponatremia, hypokalemia), hypoglycemia, Medicines (sedative-hypnotics, opiates). It is imperative to identify one of these factors so that prompt treatment given to get patient out of encephalopathy.[4-5]

The present standard of care in the management of HE is directed at decreasing the accumulation of ammonia in the hope of altering the induction of glutamate neurotoxicity and the consequent increased tone of the GABA-A receptor system in the brain.[6]Several agents have been used to address this complication of end-stage liver disease.[7]

The antibiotic neomycin tends to be effective during acute exacerbations of the syndrome, whereas metronidazole has become quite favorable for preventing HE. However, all these agents are fraught with drug related side effects and/or therapeutic compliance.[8]

Rifaximin is a derivative of rifamycin that acts by inhibiting bacterial RNA synthesis. Rifaximin is virtually unabsorbed after oral administration and exhibits broad spectrum antimicrobial activity against both aerobic and anaerobic gram-positive and gram-negative microorganisms within the gastrointestinal tract.[9] Many studies reported that rifaximin decreases ammonia plasma levels and improves the symptoms related to HE in patients with liver cirrhosis.[10]Rifaximin has a favorable profile in terms of tolerability and side effects.[11]

Patients of hepatic encephalopathy presents as medical emergency and needs immediate management. Our study is designed to find out the comparative efficacy of rifaximin versus metronidazole in these patients. Rifaximin is non-absorbable antibiotic as compared to metronidazole. I want to bring this drug in my routine practice.

OPERATIONAL DEFINITION

Hepatic encephalopathy:

Hepatic encephalopathy is defined as a spectrum of neuropsychiatric abnormalities (personality changes, (depressed level of consciousness, deterioration of GCS from 15/15 to 8/15) intellectual impairment (disoriented and confused) in patients with liver dysfunction, (deterioration of liver function tests such as bilirubian>1mg/dl, ALT >40U/L, increased prothrombin time difference from control >4 seconds, decreased albumin <3.5g/dl) after exclusion of brain disease (meningitis, encephalitis, cerebrovascular accident, malignancy).

Efficacy:

Efficacy is defined as improvement inneuropsychiatric abnormalities (personality changes (GCS 15/15), intellectual impairment in patients with liver dysfunction (Bilirubin <1mg/dl, ALT <40u/l, prothrombin time difference from control <4 seconds and serum Albumin >3.5g/dl, and a depressed level of consciousness after exclusion of brain disease (meningitis and encephalitis, cerebrovascular accident, malignancy, by CT scan brain and lumber puncture).

Material and methods:

This comparative study was conducted at Department of Medicine DHQ Teaching Hospital, Sargodha from March 2017 to September 2017 over the period of 6 months.

Inclusion Criteria:

- Patients of hepatic encephalopathy grade 3 and 4 (as operational definition).
- Both male and female.
- Age from 40 to 60 years.

Exclusion Criteria:

- Patients with brain disease. (meningitis, encephalitis, cerebrovascular accident, malignancy by CT scan, CSF examination and MRI brain)
- Diabetic ketoacidosis and renal failure. On history and lab investigation.
- Patients with septicemia. (On history and complete blood count.)

Data collection procedure:

Total 120 patients of hepatic encephalopathy grade 3, 4 was included in this study after scrutinized by inclusion criteria and after taking written consent from Institutional Review Board. Written consent was taken from every patient. All included patients was offered to pick up a slip

from total mixed up slips (half-slips was contain letter "A" and other half-slips contain letter "B") and he/she was placed in that group (Group-A or Group-B according to slip). Rifaxamin (550mg B.D) was given to patients of group A by nasogastric tube and metronidazole IV 500mg 8 hourly was given to patients of group B.

At day 7 efficacy of the both drugs was assessed as per operational definition and noted on pre-designed proforma as Yes/No.Demographic profile of all the patients was also noted on the proforma.

Data analysis procedure:

The data was entered in SPSS V16 for statistical analysis. Quantitative variable like age was presented as mean ± SD, while qualitative variable like gender, efficacy (Yes/No) was presented in frequency and percentages. Chi-square test was applied to compare the frequency of efficacy in both groups. Stratification was done for age and gender. Post stratification. Chai-square test was applied to see the level of significance.P-values $\leq$ 0.05 was considered statistically significant.

RESULTS

Total 120 patients (60 patients in each group) with HE were selected for this study. Mean age of the patients was 49.43 ± 6.866 years, mean age in group A was 49.37 ± 6.757 years and mean age in group B was 49.50 ± 7.029 years.Out of 60 patients of group A, efficacy of treatment was noted in 14 (23.33%) patients and out of 60 patients of group B, treatment was found effective in 45 (75%) patients. Significantly higher rate of efficacy was noted in patients of group A as compared to group B with p value 0.000. (Table 1)

Two age groups were made age group 40-50 years and age group 51-60 years. In age group 40-50 years, out of 30 patients of group A, efficacy of treatment was noted in 8 (26.67%) patients and out of 30 patients of group B, efficacy was noted in 23 (76.67%) patients and the difference of efficacy between the both groups was significant with p value 0.000. In age group 51-60 years, efficacy of treatment was noted in 6 (20%) and 22 (73.33%) patients and the difference was statistically significant with p value 0.000. (Table 2)Out of 39 male patients of group A and 31 male patients of group B, treatment was found effective in 11 (28.21%) patients and 21 (67.74%) patients. Difference of efficacy was significant with p value 0.001. Among the 21 female patients of group A and 29 female patients of group B, treatment was found effective in 3 (14.29%) patients and 24 (82.76%) patients and difference was statistically significant with p value 0.000. (Table 3)Total 32 of group A and 32 patients of group B was found with grade 3 HE. Efficacy of treatment was found effective in 8 (25%) patients and 24 (75%) patients and the difference of efficacy was statistically significant with p value 0.000. Total 28 patients of group A and 28 patients of group B was found with grade 4 HE. Treatment was found effective in 6 (21.43%) patients and 21 (75%) patients and the difference was statistically significant with p value 0.000. (Table 4)

Table 1: Comparison of efficacy between both groups

Group	Efficacy		Total	P value
	Yes	No		
A (Rifaxamin)	14 (23.33)	46 (76.67)	60	**0.000**
B (Metronidazole)	45 (75)	15 (25)	60	

Table 2: Comparison of efficacy between both groups for age groups

Group	Efficacy		Total	P value
	Yes	No		
age group 40-50 years				
A	8 (26.67)	22 (73.33)	30	**0.000**
B	23 (76.67)	7 (23.33)	30	
age group 51-60 years				
A	6 (20)	24 (80)	30	**0.000**
B	22 (73.33)	8 (26.67)	30	

Table 3: Comparison of efficacy between both groups for gender

Group	Efficacy		Total	P value
	Yes	No		
Male Patients				
A	11 (28.21)	28 (71.79)	39	**0.001**
B	21 (67.74)	10 (32.26)	31	
Female Patients				
A	3 (14.29)	18 (85.71)	21	**0.000**
B	24 (82.76)	5 (17.24)	29	

Table 4: Comparison of efficacy between both groups for HE grade 3& 4

Group	Efficacy		Total	P value
HE grade 3				
A	8 (25)	24 (75)	32	**0.000**
B	24 (75)	8 (25)	32	
HE grade 4				
A	6 (21.43)	22 (78.57)	28	**0.000**
B	21 (75)	7 (25)	28	

DISCUSSION

HE represents a challenging clinical complication of liver insufficiency and presents with a wide spectrum of neuropsychiatric symptoms that range from mild disturbances in cognitive function to coma.[12] The pathogenesis of this complex syndrome is thought to be multifactorial, but a key role is played by circulating gut-derived toxins such as ammonia.[13] With appropriate medical treatment, most clinical manifestations of HE are reversible when the precipitating factors are corrected.

Total 120 patients (60 patients in each group) with HE were selected for this study. Mean age of the patients was 49.43 ± 6.866 years, mean age in group A was 49.37 ± 6.757 years and mean age in group B was 49.50 ± 7.029 years.Out of 60 patients of group A, efficacy of treatment was noted in 14 (23.33%) patients and out of 60 patients of group B, treatment was found effective in 45 (75%) patients. Significantly

higher rate of efficacy was noted in patients of group A as compared to group B with p value 0.000.

In one study, rifaximin found effective in 22.1% cases for the treatment of hepatic encephalopathy.[14]In other study metronidazole found effective in 78% patients.[15]findings of these studies are comparable with the findings of our study.In an open label prospective controlled trial was conducted on patients with an acute episode of HE who were randomly divided into metronidazole-group (M-group) and rifaximin-group (R-group) with 60 patients in each. The main outcome measure was the clinical improvement of HE. Both M-group and R-group were comparable as regards age and sex (mean age 51□±□11□years and 49□±□12; male/female ratio 45:15 and 50:10, respectively). Forty-six patients (76.7%) in M-group compared with forty-five (75%) in R-group showed clinical improvement (p□=□0.412).[16]In one study by Mas et al, rifaximin found effective in 81.6% patients for the management of HE.[17]Rifaximin has proven in previous studies to be effective in the treatment of acute episodes of HE. Paik et al. reported the effectiveness of rifaximin in improving the HE episodes in about 80% of patients and lowering ammonia significantly in more than 75% of patients.[18] Also, in a randomized, double-blinded controlled trial of Sharma et al., rifaximin plus lactulose was superior to lactulose alone.[19] These observations are in favour of rifaximin as a golden player in managing acute episodes of HE. On the other hand, and surprisingly there are little data available on metronidazole in HE and there is no head-to-head comparison between these two drugs in the management of HE. Therefore, the importance of our results which show metronidazole superior to rifaximin in a limited resource setting as a short term management to avoid the potential adverse events of its long-term use because of its comparable efficacy with less costs.

CONCLUSION

In this study efficacy of treatment was significantly higher in patients managed with Metronidazole as compared to patients managed with Rifaxamin. Statistically significant association of efficacy with age and gender are noted.

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