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Research Article

Comparison between metronidazole and rifaxaminfor the management of hepatic encephalopathy

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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 randomized controlled trial was conducted at Department of Medicine DHQ Teaching Hospital, Sahiwal from October 2016 to March 2017 over the period of 6 months. Total 160 cases of HE grade 3 & 4 were selected. Two equal groups A & B were made. Group A was managed withmetronidazole and Group B was managed with rifaximin. Efficacy of both drugs was compared.

Results: Total 160 patients with HE were selected and divided into two equal groups A (Metronidazole group)& B (Rifaxamin group). Mean age of the patients was 49.45 ± 6.88 years. In group A, Metronidazole found effective in 22 (27.5%) patients for the management of HE. In group B, patients were managed with Rifaxamin and found effective in 61 (76.25%). Rifaxamin was found more effective as compared to Metronidazole for the management of HE and the difference was statistically significant with p value 0.000.

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

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

INTRODUCTION

Hepatic encephalopathy (HE) is a well known neuropsychiatric syndrome occurring in patients with either acute or chronic liver diseases, and it is characterized by disturbances in consciousness, personality and intellectual capacity, high blood ammonia levels, altered neuromuscular activity and abnormalities in the electroencephalogram (EEG). Hepatic encephalopathy (HE) is a reversible neuropsychiatric and functional syndrome occurring in 50%-70% of patients with advanced liver disease.

The symptoms of HE, manifested on a continuum, are deterioration in mental status, with psychomotor dysfunction, impaired memory, increased reaction time, sensory abnormalities, poor concentration, disorientation, even coma, and death [4, 5]. Overt HE means high mortality and poor prognosis.

For both acute and chronic HE, the mainstay treatment has been the use of non-absorbable disaccharides[3] since they decrease the absorption of ammonia through cathartic effects and by altering the colonic pH[6]. Several oral antibiotics such as neomycin, paromomycin, metronidazole, vancomycin and rifaximin have shown some degree of effectiveness in lowering serum ammonia concentration by reducing the intestinal flora responsible for its production[8].

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 clinical improvement in cases of HE managed with rifaximinand metronidazole.

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 randomized controlled trial was conducted at Department of Medicine DHQ Teaching Hospital, Sahiwal from October 2016 to March 2017 over the period of 6 months. Total 160 patients with HE grade 3 and grade 4 having age 40-60 years wither male or female were selected. Patients with brain disease, patients with diabetic ketoacidosis and renal failure on history and lab investigation patients with septicemia were excluded from the study. An approval was taken from the institution review committee. Selected patients were randomly divided into two groups A and B. Metronidazole IV 500mg 8 hourly was given to patients of group A and Rifaxamin (550mg B.D) was given to patients of group B by nasogastric tube. At day 7 clinical improvement in HE was assessed and findings was noted in pre-designed proforma along with demographic profile of the patients.

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.

All the collected data was entered in SPSS version 18 and analyzed. Mena and SD was calculated numerical data and frequencies were calculated for categorical data.

RESULTS

Total 160 patients with HE were selected and divided into two equal groups A (Metronidazole group)& B (Rifaxamin group). Mean age of the patients was 49.45 ± 6.88 years. In group A, Metronidazole found effective in 22 (27.5%) patients for the management of HE. In group B, patients were managed with Rifaxamin and found effective in 61 (76.25%). Rifaxamin was found more effective as compared to Metronidazole for the management of HE and the difference was statistically significant with p value 0.000. (Table 1)

Minimum of the patients was 40 years and maximum age was 60 years. Patients were divided into two equal age groups, age group 40-50 years and age group 51-60 years. In age group 40-50 years, clinical improvement of HE was noted in 13 (33.33%) patients of study group A while in 32 (78.05%) patients of study group B and the difference was statistically significant with p value 0.000. In age group 51-60 years, clinical improvement was noted in 9 (21.95%) patients and 29 (74.36%) patients respectively in study group A and B and the difference was statistically significant with p value 0.000. (Table 2)

Total 17 (32.69) male patients of study group A and 28 (68.29) male patients of study group B improved clinically after managed with metronidazole. The difference was statistically significant. Clinical improvement was noted in 5 (17.86) female patients of study group A while in 33 (84.62) patients of study group B. Difference of clinical improvement between the both groups was statistically significant. (Table 3)

Total 44 (55) patients of study group A and 43 (53.75) patients of study group B found with grade 3 HE. Clinical improvement in HE was noted in 13 (29.55) patients of study group A and in 33 (76.74) patients of study group B and the difference was statistically significant with p value 0.000. Grade 4 HE was noted in 36 (45) patients of study group A and in 37 (46.25) patients of study group B. Clinical improvement was noted in 9 (25) patients and 28 (75.68) patients respectively in study group A and B and the difference was statistically significant with p value 0.000. (Table 4)

able 1: Comparison of efficacy between both groups

Group	Efficacy		Total	P value
	Yes	No		
A (Metronidazole)	22 (27.5)	58 (72.5)	80	**0.000**
B (Rifaxamin)	61 (76.25)	19 (23.75)	80	

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

Group	Efficacy		Total	P value
	Yes	No		
age group 40-50 years				
A	13 (33.33)	26 (66.67)	39 (48.75)	**0.000**
B	32 (78.05)	9 (21.95)	41 (51.25)	
age group 51-60 years				
A	9 (21.95)	32 (78.05)	41 (51.25)	**0.000**
B	29 (74.36)	10 (25.64)	39 (48.75)	

Table 3: Comparison of efficacy between both groups for gender

Group	Efficacy		Total	P value
	Yes	No		
Male Patients				
A	17 (32.69)	35 (67.31)	52 (65)	**0.001**
B	28 (68.29)	13 (31.71)	41 (51.25)	
Female Patients				
A	5 (17.86)	23 (82.14)	28 (35)	**0.000**
B	33 (84.62)	6 (15.38)	39 (48.75)	

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

Group	Efficacy		Total	P value
HE grade 3				
A	13 (29.55)	31 (70.45)	44 (55)	**0.000**
B	33 (76.74)	10 (23.26)	43 (53.75)	
HE grade 4				
A	9 (25)	27 (75)	36 (45)	**0.000**
B	28 (75.68)	9 (24.32)	37 (46.25)	

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 160 patients with HE were selected and divided into two equal groups A (Metronidazole group)& B (Rifaxamin group). Mean age of the patients was 49.45 ± 6.88 years. In group A, Metronidazole found effective in 22 (27.5%) patients for the management of HE. In group B, patients were managed with Rifaxamin and found effective in 61 (76.25%). Rifaxamin was found more effective as compared to Metronidazole for the management of HE and the difference was statistically significant 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 rifaximin superior to metronidazole 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 Rifaximin as compared to patients managed with Metronidazole. Statistically significant association of efficacy with age and gender are noted.

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