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Original Research Article

Comparative Efficacy of Rifaxamin vs Metronidazole in the Treatment of Hepatic Encephalopathy

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Abstract

Hepatic encephalopathy (HE) describes a wide spectrum of often-reversible neuropsychiatric abnormalities that occur in patients with acute or chronic liver disease. Currently, the mainstay treatment of HE includes; non-absorbed disaccharides (like lactulose) and non-absorbable antibiotics (ex. rifaximin). Metronidazole is one of the alternative treatment options for acute HE. Thus we performed open label randomized controlled trial to compare efficacy of rifaximin and metronidazole. This is an open label randomized controlled trial in which cirrhotic patients irrespective of etiology was enrolled. The symptoms of HE were graded according to West Haven Criteria (WHC) at baseline and after 7 days of treatment. Patients were allocated in two groups; Rifa and Metro groups, and were subjected to rifaximin and metronidazole respectively in addition to lactulose. Treatment efficacy and adverse affects in both the groups were calculated. Total 120 subjects with HE (grade- III or IV) were selected, 60 subjects were subdivided into each group. Out of 60 subjects of Rifa group, efficacy of treatment was noted in 14 (23.33%) patients and out of 60 subjects of Metro Group, treatment was found effective in 45 (75%) patients with p value of 0.0001. The conclusion of this study is that efficacy of metronidazole is superior to rifaximin in managing acute episode of hepatic encephalopathy due to decompensated liver cirrhosis. Hence, its use is recommend in poor resource settings, because of its lower cost and good safety margin.

Keywords: Hepatic encephalopathy, Lactulose, Rifaximin, Metronidazole

INTRODUCTION

Hepatic encephalopathy describes a wide spectrum of often-reversible neuropsychiatric abnormalities that occur in patients with acute or chronic liver disease (Wakim-Fleming, 2011; Lewis and Howdle, 2003). The pathophysiology of HE is complex and it manifests with progressive deterioration of the superior neurological functions. HE occurs in the presence of insufficient hepatic clearance of toxins absorbed from the intestine resulting in neurochemical abnormalities across the blood brain barrier (Abou-Assi and Vlahcevic, 2001). 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 (Hepatic encephalopathy, 2014).

Hepatic encephalopathy can develop due to many factors which include gastro-intestinal bleeding, infections, constipation, electrolyte imbalance (hypo-natremia, 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. (Abrams and Fallon, 2001; Assy et al., 1999).

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 (Zeneroli et al., 2005). Several agents have been used to address this complication of end-stage liver disease (Prasad et al., 2007). This is done by introducing agents that reduce or inhibit production of intestinal ammonia or minimize its absorption from the gastrointestinal tract as well as correcting precipitating factors such as gastrointestinal hemorrhage, electrolyte imbalances and constipation (Eltawi et al., 2012).

For both acute and chronic HE, the mainstay treatment has been the use of non-absorbable disaccharides since they decrease the absorption of ammonia through cathartic effects and by altering the colonic pH (Maclayton and Eaton-Maxwell, 2009). 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. The antibiotic neomycin tends to be effective during acute exacerbations of the syndrome, whereas metronidazole has become quite favourable for preventing HE. However, all these agents are fraught with drug related side effects and/or therapeutic compliance (Maclayton and Eaton-Maxwell, 2009).

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 micro-organisms within the gastrointestinal tract (Bass et al., 2010). Many studies reported that rifaximin decreases ammonia plasma levels and improves the symptoms related to HE in patients with liver cirrhosis (Bajaj et al., 2011). Rifaximin has a favorable profile in terms of tolerability and side effects (Williams and Bass, 2005).

Thus we planned a study to compare efficacy of rifaxamin and metronidazole for the treatment of hepatic encephalopathy grade III and IV

MATERIAL AND METHODS

This is an open label randomized controlled trial conducted in the Department of Medicine Bahawal Victoria Hospital Bahawalpur, Pakistan from Jan 2018 to July 2018.

Inclusion criteria was all cirrhotic patients irrespective of etiology, with age 40-60 years; admitted with acute onset of grade-III to IV hepatic encephalopathy admitted in the Department of Medicine, Bahawal Victoria Hospital, Bahawalpur; from Jan 2018 to July 2018 were enrolled.

Exclusion criteria was patients with brain disease (meningitis, encephalitis, cerebrovascular accident, malignancy by CT scan, CSF examination and MRI brain); Diabetic ketoacidosis, renal failure, and/or with sepsis were excluded.

The symptoms of HE were graded according to West Haven Criteria (WHC) (14) by the primary investigator at time of presentation, during and after the starting treatment.

Sample Size

Sample size was calculated as 120 patients with the use of WHO calculator considering efficacy of Rifaximin (Rifa group) as 22.1% and Metronidazole (Metrogroup) as 78%. The power of study was taken as 90%. The calculated sample size was 120, so 60 participants were allocated in each group.

The primary endpoint of study was improvement in severity of HE using West Haven Criteria after 7 days of admission. Possible adverse events were recorded throughout the study period.

Ethical Approval

The study was approved by Institutional Ethical Review Board. Informed written consent was taken from attendants of every patient. Patients in Rifa group were treated with Rifaximin (550mg B.D) through nasogastric tube and while Metro Group patients were treated with Metronidazole IV 500mg 8 hourly. In addition, both groups received a concomitant fixed basic regimen of oral lactulose (15–30 ml) 2–3 times/day till the passage of 2–3 loose stools daily.

The data was entered in statistical Package for Social Sciences, version 19 (SPSS Inc., Chicago, Illinois, USA) for 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. Effect modifier like age and gender were controlled through stratification. P-values ≤ 0.05 were considered statistically significant.

RESULTS

A total of 120 patients (60 patients in each group) with HE (grade- III or IV) were selected for the study. Mean age of the patients was 49.43 ± 6.866 years, mean age in Rifa group was 49.37 ± 6.757 years and mean age in Metro group was 49.50 ± 7.029 years. Baseline characteristics are depicted in table 1.

Table 1. Baseline characteristics of study population

Variable	Mean ± SD
Age (years)	49.43 ± 6.86
Rifa group	49.37 ± 6.75
Metro group	49.5 ± 7.03
Gender (M / F)	60 / 60
Rifa group	39/ 21
Metro group	31 / 29
Hepatic Encephalopathy	
Grade III	
Rifa group	32
Metro group	32
Grade IV	
Rifa group	28
Metro group	28

Table 2. Comparison of efficacy between both groups

Treatment group	Hepatic Encephlopathy		Total	P value
	Improved	Not improved		
Rifa Group	14 (23.3)	46 (76.7)	60	0.000
Metro Group	45 (75.0)	15 (25.0)	60	

Table 3. Comparison of efficacy among different groups

Variable		Group	Efficacy		Total	P value
			Yes	No		
Age	40-50 years	Rifa	8 (26.67)	22 (73.33)	30	0.000
		Metro	23 (76.67)	7 (23.33)	30	
	51-60 years	Rifa	6 (20)	24 (80)	30	0.000
		Metro	22 (73.33)	8 (26.67)	30	
Gender	Male	Rifa	11 (28.21)	28 (71.79)	39	0.001
		Metro	21 (67.74)	10 (32.26)	31	
	Female	Rifa	3 (14.29)	18 (85.71)	21	0.000
		Metro	24 (82.76)	5 (17.24)	29	
Grades of HE	Grade 3	Rifa	8 (25)	24 (75)	32	0.000
		Metro	24 (75)	8 (25)	32	
	Grade 4	Rifa	6 (21.43)	22 (78.57)	28	0.000
		Metro	21 (75)	7 (25)	28	

Out of 60 patients of Rifa group, efficacy of treatment was noted in 14 (23.33%) patients and out of 60 patients of Metro group, treatment was found effective in 45 (75%) patients. Significantly higher rate of efficacy was noted in patients of Metro group as compared to Rifa group with p value 0.000 as shown in table 2.

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 Rifa group, efficacy of treatment was noted in 8 (26.67%) patients and out of 30 patients of Metro group, 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.

Out of 39 male patients of Rifa group and 31 male patients of Metro group, 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 Rifa group and 29 female patients of Metro group, treatment was found effective in 3 (14.29%) patients and 24 (82.76%) patients and difference was statistically significant with p value 0.000.

Total 32 of Rifa group and 32 patients of Metro group 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. While 28 patients of Rifa group and 28 patients of Metro group 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 3 shows comparison of different groups and p values. No adverse event or death was reported during the study.

DISCUSSION

Four pronged approach is recommended by international societies of liver diseases (Vilstrup et al., 2014) which includes urgent initiation of care for patients with altered level of consciousness (ALOC), alternative causes of loss of consciousness should be ruled out, identification of precipitating factors and their correction, and to commence empirical HE treatment. Currently, the mainstay treatment of HE includes; non-absorbed disaccharides (like lactulose) and non-absorbable antibiotics (ex. rifaximin) (Leise et al., 2014). Metronidazole is one of the alternative treatment options for acute HE (Vilstrup et al., 2014).

Thus we performed open label randomized controlled trial to compare efficacy of rifaximin and metronidazole. Our hypothesis of rifaximin is superior to metronidazole in terms efficacy in overt hepatic encephalopathy was rejected. As our study results were in favor of metronidazole with significant p value. This result is contrary to the observation by Mekky et al. (2018) in which they found both the drugs were of equal efficacy. In one study, rifaximin found effective in 22.1% cases for the treatment of hepatic encephalopathy (Bass et al., 2010). This is an option expensive while according to other study (Morgan et al., 1982), metronidazole is effective in 78% patients. Moreover, its much cheaper option than rifaximin. Thus in the setting of limited resources, metronidazole is effective option in terms of efficacy and cost effectiveness.

The long term use of metronidazole is associated with ototoxicity, nephrotoxicity, neurotoxicity and reversible encephalopathy (Vilstrup et al., 2014). In patients with decompensated liver disease, metabolism of metronidazole is affected which results into decreased hepatic clearance and increased concentration of cerebrospinal fluid leading to toxicity at a relatively low total cumulative dose of 22 g. While classical features of metronidazole-induced encephalopathy (MIE) seen on MRI brain shows bilateral basal dentate nuclei hyper intensities on T2 images. (17, 18).Hence the long term use of metronidazole is not recommended by EASL and ASSLD (Vilstrup et al., 2014).

There are some limitations of our study like open-label design with small sample size and a single center study. Furthermore, we did not categorize the patient according to etiology of cirrhosis and severity of liver cirrhosis was not assessed. There is also another weak point in our enrolled patients, all of them were in higher grade of HE. This observation limits the generalization of our recommendation to cover all HE grades.

CONCLUSION

We conclude that efficacy of metronidazole is superior to rifaximin in managing acute episode of hepatic encephalopathy due to decompensated liver cirrhosis. Hence, we recommend its use in resource poor settings, because of its lower cost and good safety margin. Moreover, studies with larger sample size are warranted to demonstrate the effect of different drug regimens in comparison to their safety, clinical course, recurrence of HE and long term usage.

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