



## Comparison of current and emerging strategies for treating hepatic encephalopathy.

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**ABSTRACT... Objective:** To compare the efficacy of rifaximin and metronidazole which are the most commonly used antibiotics used in treating this disorder. **Study Design:** Randomized Controlled Trial. **Setting:** Department of Medicine, Sharif Trust Hospital. **Period:** Jan 2018 to July 2018. **Material & Methods:** In this study cirrhotic patients irrespective of etiology were enrolled. West Haven Criteria (WHC) was utilized for grading the symptoms of HE at baseline and after 7 days of treatment. The study subjects were further subdivided into two groups: rifa group and metro group, and were given rifaximin and metronidazole respectively along with lactulose. The efficacy of the treatment and adverse effects in both the groups were estimated. **Results:** Total 180 subjects with HE (grade- III or IV) were selected, 90 subjects were subdivided into each group. Out of 90 subjects of Rifa group, efficacy of treatment was noted in 14 (15%) patients and out of 90 subjects of Metro Group, treatment was found effective in 45 (50%) patients with p value of 0.0001. **Conclusion:** The conclusion of this study is that metronidazole is superior to rifaximin in terms of efficacy in the management of an acute phase of hepatic encephalopathy due to chronic liver cirrhosis. Hence, due to its cheaper cost and a good safety margin its use is recommend in poor resource settings.

**Key words:** Hepatic Encephalopathy, Metronidazole, Lactulose, Rifaximin.

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## INTRODUCTION

Hepatic encephalopathy (HE) is a combination of metabolic disorders ranging from hepatic impairment and progressing up to neuropsychiatric manifestations<sup>3</sup> The factors causing HE include bleeding and infections of the gastrointestinal tract, constipation, hypoglycemia, electrolyte imbalances, certain medications which include opiates and sedative-hypnotics. Cirrhotic patients usually have a bad nutritional status due to anorexia, nausea, malabsorption, and an altered metabolism.<sup>6</sup> The poor dietary status due to anorexia leads to a deficiency of branched chain amino acids and result in accumulation of aromatic amino acids, both worsening protein-energy malnutrition and glutaminergic neurotransmission.<sup>10</sup> Major part of the ammonia production in the gut is by the deamination of dietary amino acids by intestinal bacteria and some contribution is also made

by urease-positive bacteria. Prompt detection and treatment of these factors can lead to lower morbidity status in these patients.<sup>4</sup>

Presently the main target of management of HE is to decrease the levels of ammonia in order to stop the induction of glutamate neurotoxicity.<sup>6</sup> Many therapeutic agents have been used for the treatment of these complications of end-stage liver disease.<sup>7</sup> These medications reduce the formation of ammonia by reducing its absorption from the gastrointestinal tract. The aggravating factors like electrolyte imbalances, constipation and gastrointestinal hemorrhage are also corrected.<sup>20</sup>

The mainstay treatment for acute and chronic HE is the use of non-absorbable disaccharides like lactulose because they decrease the absorption of ammonia through from the small

intestine by altering the pH of the colon. Which is a carbohydrate passes through the small bowel without being digested.<sup>21</sup> In the colon fermentation of lactulose by anaerobic bacteria takes place. The fermentation of lactulose yields weak acids and gases which leads to alteration of the pH of the colon which causes the acidification of ammonia resulting in formation of ammonium ion which is poorly absorbed.<sup>8</sup> Some oral antibiotics like paromomycin, neomycin, vancomycin, metronidazole and rifaximin are also effective in lowering the serum ammonia levels by decreasing the gut flora. Neomycin is an antibiotic which is effective during acute phase of the syndrome. However metronidazole is commonly used for the prevention and treatment of hepatic encephalopathy. These therapeutic agents are associated with adverse effects and also therapeutic compliance.<sup>16</sup> Thus the treatment of HE is dependent on its severity. Treatment of causative factor is the first line of treatment as majority of the patients develop HE because of a precipitating factor. Treatment of acute changes in the mental status is the next step. Lastly secondary prophylaxis is given to stop the recurrence of HE. The treatment options for HE are limited. Commonly used medications are rifaximin and lactulose. Second line treatment options include probiotics, branched chain amino acids and ammonia scavengers.<sup>14,17,20</sup>

Rifaximin which is derived from rifamycin, acts by inhibiting the synthesis of the bacterial RNA. Rifaximin is a broad spectrum antibiotic and acts against both the aerobic and anaerobic gram-positive and negative microorganisms within the gastrointestinal tract.<sup>9</sup> Previous studies have reported that rifaximin reduces the plasma ammonia concentration and leads to improvement in the symptoms of hepatic encephalopathy in patients suffering from liver disease.<sup>10,14</sup> Rifaximin has is more favorable therapeutic option in terms of tolerability and side effects.<sup>18</sup>

This study was planned for comparing the efficacy of rifaximin and metronidazole in the management of hepatic encephalopathy.

## MATERIAL & METHODS

This study is an open label randomized controlled trial conducted in the Department of Medicine, in a private sector teaching hospital in Lahore Pakistan from Jan 2018 to July 2018. it was reviewed and approved by Ethical Research Board 9SMDC/SIAHS/441).

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, Sharif Trust Hospital; Lahore from Jan 2018 to July 2018 were enrolled.

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

The study subjects included patients older than 40 years diagnosed with chronic liver disease along with development of reversible neurological decline. The effectiveness of the treatment regime was estimated by the number of patients who had shown clinical improvement of the symptoms of HE during the course of treatment. To estimate the neurological response, mental status scoring was done by using Conn's classification. According to this classification subjects were graded as grade 0 to 4. Grade 0 consisted of patients with no personality or behavioral abnormality. Grade 1 patients had disorientation, shortened attention span, anxiety or euphoria, or inability to add or subtract. Grade 2 subjects had disorientation in time, personality change or inappropriate behavior along with lethargy. Grade 3 subjects were those who had gross disorientation, confusion or bizarre behavior, somnolence, responsiveness to stimuli. Grade 4 subjects were those who had coma.

The asterixis was graded according to the established criteria as: Grade 0 with no tremors, grade 1 with few flapping motions grade 2 had occasional flapping motions, grade 3 with frequent flapping motions and grade 4 with almost continuous flapping motions.

### Sample Size

A sample size of 180 patients was calculated by using WHO calculator for sample size considering efficacy of Rifaximin (Rifa group) as 22.1% and Metronidazole (Metro group) as 78%. The calculated sample size was 180, so 90 participants were allocated in each group.

The improvement in severity of HE was calculated using West Haven Criteria after 7 days of admission. The patients were strictly monitored for any adverse effects throughout the study.

The patients in the Rifa group were given Rifaximin dose of 550mg B.D and the patients in the Metro Group were given Injection Metronidazole 500 mg IV 8 hourly. In addition, the subjects of both the groups were also given a concomitant regimen of lactulose orally (dosage 15–30 ml) two to three times per day.

The data was entered in SPSS software, version 21. Quantitative variable like age was presented as mean ± SD, while qualitative variable like gender, efficacy (Yes/No) was presented in frequency and percentages. To compare the frequency of efficacy in both groups Chi-square test was used. Effect modifier like age and gender were controlled through stratification. A P-value of ≤ 0.05 was considered to be significant statistically.

### RESULTS

A total of 180 patients (90 patients in each group) with HE (grade- III or IV) were selected for the study. The mean of ages in both the groups was 49.43 ± 6.866 years.

In Rifa group the treatment efficacy was seen in 14 (23.33%) patients and in Metro group, treatment was found effective in 45 (75%) patients. The rate of efficacy was significantly higher in Metro group

as compared to Rifa group with p value 0.000.

With respect to age our results revealed that in age group 40-50 years efficacy of treatment was noted in 6 (13.33%) patients in Rifa group and in 39 (86.66%) of the patients in metro group. In 51-60 years age group, a statistically significant difference in treatment efficacy was noted in 8 (17.77%) and 27 (60%) patients in Rifa and metro groups with a p value 0.000.

A total of 32 subjects of Rifa group and 32 patients of Metro group was found with grade 3 Hepatic encephalopathy. Efficacy of treatment was seen in 8 (25%) patients and 24 (75%) patients respectively and the difference was statistically significant with p value 0.000. A total of 28 patients of Rifa group and 28 patients of Metro group was found with grade 4 Hepatic encephalopathy. Efficacy of treatment was noted in 6 (21.43%) subjects of Rifa group and 21 (75%) patients in metro group with a p value 0.000.

Variable	Mean ± SD
Age (years)	46.42 ± 12.75
Rifa group	46.37 ± 12.75
Metro group	46.5 ± 10.03
Gender (M / F)	90 / 90
Rifa group	37 / 23
Metro group	33 / 27
Hepatic Encephalopathy	
Grade III	
Rifa group	32
Metro group	32
Grade IV	
Rifa group	28
Metro group	28

**Table-I. Anthropometric and baseline variables of study population.**

Treatment Group	Hepatic Encephalopathy		Total	P-Value
	Improved	Not Improved		
Rifa Group	14 (15)	76 (84.4)	90	0.000
Metro Group	50 (55)	40 (45)	90	0.000

**Table-II. Comparison of efficacy between both groups.**

Variable		Group	Efficacy		Total	P-Value
			Yes	No		
Age	40-50 years	Rifa	6 (13.33%)	39(86.66%)	45	0.000
		Metro	23 (51.1%)	22 (48.8%)	45	
	51-60 years	Rifa	8 (17.77%)	37(82.22%)	45	0.000
		Metro	27 (60)	18(40)	45	
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	

Table-III. Comparison of efficacy among different groups.

## DISCUSSION

Hepatic encephalopathy is a clinical complication of chronic liver disease and has a wide spectrum of neuropsychiatric symptoms. These symptoms range from mild abnormality in the cognitive function to coma to even death.<sup>14</sup> Traditionally, the first-line therapy for HE was non-absorbable disaccharides.<sup>14</sup> The adjustment of disaccharide dose in order to get two to three bowel movements per day often leads to side effects like nausea, vomiting, flatulence and poor drug compliance.<sup>13</sup> Oral antibiotics such as neomycin, vancomycin or paromomycin are more useful than disaccharides and have less side effects, but have a risk of toxicity.<sup>13,16</sup> Due to this risk of toxicity, these agents are not commonly used in clinical practice now a days.<sup>19</sup>

Our hypothesis that rifaximin is better than metronidazole with respect to efficacy in treatment of hepatic encephalopathy was rejected as our study results came out in favor of metronidazole with significant p value. This result is contrary to the observation by Mekky A et.<sup>15</sup> in which they found both the drugs were of equal efficacy. In one study, rifaximin was found effective in 22.1% cases of hepatic encephalopathy.<sup>12</sup> While according to another study<sup>13</sup>, metronidazole is effective in 78% patients.

With respect to age our results revealed that metronidazole is a better treatment option in both age groups. These findings are similar to the findings of Ridola et al.<sup>4</sup>

Rifaximin is an antibiotic that is effective in the

management of hepatic encephalopathy with minimum side effects.<sup>19</sup> It is well tolerated with minimum risk of developing bacterial resistance. In order to compare efficacy of rifaximin and metronidazole we performed an open label randomized controlled trial. In our study 75% patients of metro group showed clinical improvement in signs and symptoms of hepatic encephalopathy as compared to 23.3% in the rifa group. Moreover, it is a much cheaper option than rifaximin. Thus in the setting of limited resources, metronidazole is effective option in terms of efficacy and cost effectiveness.

The prolonged use of metronidazole is associated with ototoxicity, nephrotoxicity, neurotoxicity and reversible encephalopathy.<sup>14</sup> 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.<sup>17,18</sup> Hence the long term use of metronidazole is not recommended.<sup>14</sup>

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 another limitation in our enrolled patients that all of them were in higher grade of Hepatic encephalopathy. This limits the application of our recommendations to cover all Hepatic encephalopathy grades.

## CONCLUSION

Our study can be concluded that in terms of efficacy metronidazole is a better option as compared to rifaximin in the treatment of hepatic encephalopathy due to cirrhotic liver disease. Hence, its use is recommended in low resource healthcare settings because of its cheaper cost and a good margin of safety.

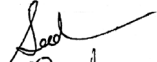

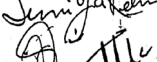


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3	Suniya Rehman	Data collection.	
4	Zara Sami	Literature review.	
5	Hasan Ali	Literature review.	
6	Irum Saddiqa	Interpretation of results.	