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DISCRIPTIVE CASE SERIES STUDY: ROLE OF RIFAXIMIN IN HEPATIC ENCEPHALOPATHY

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ABSTRACT

Background: Hepatic encephalopathy is the second most common major complication in cirrhotic patients and it significantly impacts quality of life. Medicinal approaches for hepatic encephalopathy treatment and prevention mainly depends on ammonia-lowering strategies and non-absorbable disaccharides are currently considered the cornerstone therapy. Non-absorbable antibiotics, such as neomycin and paramycin, are effective in treatment of acute hepatic encephalopathy episodes but their prolonged use has serious side-effects. To overcome these limitations, rifaximin use has been proposed. **Objective:** To determine the efficacy of rifaximin in cases of chronic liver disease presenting with hepatic encephalopathy. **Methodology:** In this descriptive cases series study, which was conducted at Department of Medicine, Jinnah Hospital Lahore from May 2017 to October 2017 for 6 months period. The cases of both genders with age range of 25–70 years, having CLD (Child Pugh Class B & C) and acute hepatic encephalopathy of grade II or more irrespective of the cause were included in this study. Hepatic encephalopathy was labeled according to the West Haven Criteria. The cases of hepatic encephalopathy were given Rifaximin in a dose of 550 thrice a day for 7 days and complete resolution of hepatic encephalopathy at 7th day was labeled as positive efficacy. Data was analyzed by using SPSS 20. **Results:** In this study, there were total 254 cases out of which 144 (56.6%) were males and 110 (43.33%) females. There were 104 cases in Child Pugh class B and 150 cases in Child Pugh class C. Efficacy of rifaximin was seen in 129 (50.7%) cases. The efficacy was significantly high in cases that had Child Pugh Class B. Efficacy was also significantly better in grade II encephalopathy 62/86 cases in contrast to 53/71 cases with grade III. **Conclusion:** Rifaximin is good antibiotic for gut flora but it relieves hepatic encephalopathy in only half of cases. It is significantly better in cases with Child pugh class B and with encephalopathy grade III.

KEYWORDS: Chronic liver disease, Rifaximin, West Haven Criteria, Hepatic Encephalopathy. Child Pugh class, Efficacy.

INTRODUCTION

Hepatic encephalopathy is the second most common complication in liver cirrhosis following ascites.[1] Hepatic encephalopathy is an important factor even in the progression of liver disease. It exerts formidable effect on quality of life of patient and caregivers and increase hospitalization rates with considerable economic impact. It occurs in the presence of insufficient hepatic clearance of toxins absorbed from intestine. Hepatic encephalopathy is a complex neuropsychiatric syndrome manifested as general depression of the central nervous system in the form of impaired memory, poor concentration, disorientation, psychiatric problems, neuromotor signs and symptoms (aterixis, hyper-reflexia, rigidity, myoclonus) and deep coma etc.[2,3,4] There are many factors that play important role in hepatic encephalopathy pathogenesis including mercaptans, endorphins, glutamate, benzodiazepines agonist, tryptophan, zinc deficiency and indole etc.[5,6,7] Among all these factors, plasma ammonia remains key factor.[8] There are many theories regarding its pathogenesis but most important is ammonia theory, that there is increase production of ammonia by gut flora that decreases detoxification capabilities of liver and crosses blood brain barrier and effects brain in multiple ways. Multiple treatment options have been tried including enema, lactulose, neomycin, paramycin, metronidazole and rifaximin alone or in combination. Non- absorbable disaccharides such as lactulose and lacitol have been the first line of drug for the treatment of hepatic encephalopathy. They are directed at reducing serum level of ammonia by decreasing the absorption of ammonia through cathartic effects and by altering

colonic pH.[9] Abdominal discomfort and pain, diarrhea and flatulence are the main side effects of cessation of therapy.[10] Other antibiotics like neomycin and paramycin are not recommended for long-term use because of nephrotoxicity and ototoxicity.[11,12] Rifaximin is an oral antibiotic that accumulate in GIT, has broad spectrum antimicrobial activity against gram negative, gram positive, aerobic and anaerobic enteric bacteria.[13,14] Rifaximin develops low risk of bacterial resistance in long-term use.[15] In randomized studies, rifaximin was more effective than non-absorbable disaccharides and have efficacy that is equivalent to or greater than of other antibiotic used in the treatment of acute hepatic encephalopathy.[16] Some studies showed that rifaximin is superior to lactulose and other antimicrobial in patient with mild to moderate severe hepatic encephalopathy.[17] There are several other studies also elaborated the efficacy of rifaximin over lactulose/lacitol in the treatment of acute hepatic encephalopathy.[18] Objective of this study was to determine the efficacy of rifaximin in hepatic encephalopathy.

METHODOLOGY

In this descriptive study, which was conducted at Department of Medicine, Jinnah Hospital Lahore from May 2017 to October 2017. All patients or their legally authorized representatives provided written informed consent. Ethical approval letter was taken from the Ethical review committee of our institute.

The irrespective of the genders, patients with age range of 25–70 years, having CLD (Child Pugh Class B & C) and acute hepatic encephalopathy of grade II or more irrespective of the cause were included in this study. Patients with other co morbid conditions like Diabetes mellitus, hypertension, renal, respiratory or cardiac failure and those taking sedative or psychiatric drugs were excluded from this study.

Episodes of hepatic encephalopathy that were precipitated by gastrointestinal hemorrhage requiring transfusion of at least 2 units of blood, by medication use, by renal failure requiring dialysis, or by injury to the central nervous system were not counted as previous episodes. Pregnancy and breast feeding women were excluded from the study because rifaximin can be used in both situation. The data was analyzed by using SPSS version 20. Age, duration of cirrhosis was presented as mean and standard deviation. Gender, grade of hepatic encephalopathy, child pugh class and efficacy were presented in frequency and percentages. Hepatic encephalopathy was labeled according to the West Haven Criteria. The cases of Hepatic encephalopathy were given Rifaximin in a dose of 550 mg three times a day for 7 days and complete resolution of hepatic encephalopathy at 7th day was labeled as positive efficacy. The diagnosis of hepatic encephalopathy was made and divided into following grades:

Grade I: Alert, Euphoria or anxiety, occasionally depression, shortened attention span impaired performance of addition, flapping tremor infrequent at this stage

Grade II: Lethargy, drowsiness, subtle personality change, inappropriate behavior and disorientation, flapping tremor easily elicited.

Grade III: Stuporose, but responsive to verbal stimuli confusion, incoherent speech and gross disorientation.

Grade IV: Coma (unresponsive to verbal or noxious stimuli), flapping tremor usually absent.

RESULTS

In this study, total 254 patients were enrolled in the study, out of which 144 (56.67%) were males and 130 (43.33%) females. The mean age was 58.21±5.3 years. 104 (40.9%) patients were belonged to Child Pugh class B and 150 (59.1) cases of Child Pugh class C. At the time of presentation, 86 (33.8%) were in Grade II, 71 (27.95%) cases were in Grade III and 97 (38.1%) cases were in Grade IV hepatic encephalopathy. Efficacy of rifaximin was seen in 129 (50.7%) cases. The efficacy was significantly high in cases that had Child Pugh Class B where it was seen in 75/254 (29.5%) cases as compared to 54/254 (21.5%) in class C. Efficacy of rifaximin was better in patient with Grade II hepatic encephalopathy 62/254 (24.4%) as compared to Grade III 53/254 (20.86%) and Grade IV 14/254 (5.5%).

Table 1: Baseline characteristics in study subjects (n=254) Study variables (n=254).

Variables	No. of Cases	Percentage
Male	144	56.6%
Female	110	43.3%
Child Pugh class B	104	40.9%
Child Pugh class C	150	59.1%
Hepatic encephalopathy Grade II	86	33.8%
Hepatic encephalopathy Grade III	71	27.9%
Hepatic encephalopathy Grade IV	97	38.1%

Table 2: Child Pugh class vs. efficacy.

Child Pugh Class	Efficacy	
	Yes	No
Class B	75	29
Class C	54	96
Total	129	125

Table 3: Hepatic encephalopathy Grade vs. Efficacy.

Grade	Efficacy	
	Yes	No
Grade II	62	24
Grade III	71	53
Grade IV	97	14
Total	129	125

DISCUSSION

The prevention of episodes of hepatic encephalopathy is an important goal in the treatment of patients with liver disease[19,20,21,22], especially since symptoms of overt encephalopathy are debilitating and decrease the ability for self-care, leading to improper nutrition and non-adherence to a therapeutic regimen, which in turn leads to severe symptoms, frequent hospitalizations, and a poor quality of life. Hepatic encephalopathy is a medical emergency and is the end result of various pathophysiological mechanisms as a result of different insulting events like constipation, GI bleeding, electrolyte disturbance, infections and so on. The mainstay of the treatment lies on two components, removing the insulting agent and sterilization of the gut and hence decreasing the ammonia levels. Lactulose is the most widely used and Rifaximin is the recent one used for this purpose. Our study showed that the use of rifaximin reduced the risk of a breakthrough episode of hepatic encephalopathy during a 6-month period among patients.

Efficacy of rifaxamin was seen in 129 (50.7%) cases in the present study. This was similar to studies done by Ojetti V et al in the past that also had the efficacy around 50% of their cases.[23] However, the study done by Sharma BC et al[24], where they compared it with lactulose and it was seen that lactulose had better results than this. Zullo et al[25], also were unable to prove the Rifaximin as better agent than the lactulose in the treatment of hepatic encephalopathy, however the results were not statistically significant. In the present study, the efficacy of Rifaximin in HE was significantly high in cases that had Child Pugh Class B where it was seen in 75 cases out of 129 as compared to 54 cases in class C. In a systematic review, rifaximin has been found to be at least equally effective or superior to non-absorbable disaccharides and antimicrobials in relieving signs or symptoms observed in patients with mild-to–moderately severe HE.[26] The risk of bacterial resistance appears to be lower with rifaximin than with systemic antibiotics. Both in vitro and in vivo studies of the effects of rifaximin on commensal flora suggest that rifaximin resistant organisms have low viability.[27,28] In summary, this study shows a robust protective effect of rifaximin against episodes of hepatic encephalopathy. Rifaximin also reduces the risk of hospitalization involving hepatic encephalopathy.[29,30]

CONCLUSION

Rifaximin is good antibiotic for gut flora and its bacterial resistance is very low, but it relieves hepatic encephalopathy only in half of cases. It is significantly better in cases with Child pugh class B and with encephalopathy grade II.

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