ORIGINAL ARTICLE

Compare the Efficacy of Low versus High Dose of Rifaximin for Primary Prophylaxis of Protosystemic Encephalopathy

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ABSTRACT

Objective: To differentiate the effectiveness of rifaximin in protosystemic primary prophylaxis of hepatic encephalopathy patients by using high and low dose.

Study Design: Randomized controlled trial

Place and Duration of Study: Department of Medicine, Avicenna Medical & Dental College Lahore from 1st October 2019 to 31st March 2020

Methodology: Eighty patients of both genders with liver cirrhosis diagnosed to have hepatic encephalopathy were enrolled. Patient's detailed demographics including age, gender, BMI and etiology of liver cirrhosis were recorded after taking written consent. Patients were equally divided into two groups, each group contains 40 patients, Group 1 received 200 mg dose of rifaximin twice a daily and group 2 received 550 mg of rifaximin twice a daily. Patients were followed for 6 months. Effectiveness in term of protosystemic hepatic encephalopathy and mortality were examined at the end of treatment.

Results: There were 22 (55%) males and 18 (45%) female patients in group 1 and in group 2, 20 (50%) patients was male and 20 (50%) were females. No significant difference was observed regarding mean age of patients between both groups 1 and 2 (48.76±11.38 years Vs 49.02±10.44 years). In group 1 PSE developed in 16 (40%) patients and in group 2 it was developed in 14 (35%) patients, no significant difference was found between both groups with p-value >0.05. During follow-up overall 17 patients were died, 9 (22.5%) in group 1 and 8 (20%) in group 2. There were no any significant difference found between died patients (p value 0.97).

Conclusion: The use of rifaximin either low or high dose is not effective to prevent development of protosystemic hepatic encephalopathy.

Keywords: Efficacy, Rifaximin, Prophylaxis, Prostosystemic encephalopathy

INTRODUCTION

It is well known that the development of hepatic encephalopathy (HE) impairs the cognitive role in cirrhotic patients and predisposes them to such hazards as higher felling frequency. This cognitive disability has an significant detrimental effect on the patients' quality of life.[1]

The hepatic encephalopathy is a brain condition related to the build-up of blood contaminants leading to a liver's failure to detoxify. Ammonium is a major contributor to the pathophysiology of this condition, and even the therapies currently available for HE will limit or facilitate the metabolism of extrahepatic tissues, or the development and bowel absorbtion of ammonium.[2] In addition, non Absorbable disaccharides, like lactulose, antibiotics in the intestinal lumen, such as rifaximin, and medicines that promote extrahepatical ammonium metabolism, such as L-ornithine L-aspartate (LOLA), are considered treatments that have shown their efficacy in both minimal HE (MHE), neuropsychometric changes (OHE).[3]

Hepatic Encephalopathy characterized by the severity of executive and motor deficits. Original signs include sleep rhythm reversal, apathy, hypersomnia, agitation and carelessness. Later, neurologic symptoms, such as hyperreflexia, rigidity, myoclonal disorder and asthérixis may be seen in delirium and coma.[4]The pathophysiology of HE has been ambiguous and indicates that the dominant neurological functions have been gradually impaired. The presence of incomplete hepatic clearance from toxins ingested in the stomach contributes to neurochemical malformations through the blood brain barrier.[5] Hepatic encephalopathy exists. The most widely recorded cause of HE is the elevated level of serum ammonia in 60-80 percent of patients affected.[6,7]

The function of rifaximin for secondary encephalopathy prophylaxis has been widely studied with mixed results and even at low doses has been shown to be successful, but its effectiveness for primary encephalopathy prophylaxis has not been studied much.[8,9] Few experiments have demonstrated their benefits but there were not enough evidence available to suggest their use. In addition, the effectiveness of low-dose rifaximin on primary prophylaxis must also be evaluated as against full-dose because of the high cost and few GI-linked side effects of rifaximin. The present study was conducted aimed to compare the efficacy of low dose versus high dose of rifaximin for protosystemic primary prophylaxis of hepatic encephalopathy patients.

MATERIALS AND METHODS

This randomized controlled trial was conducted at Department of Medicine, Avicenna Medical & Dental College Lahore from 1st October 2019 to 31st March 2020. A total of 80 patients of both genders with liver cirrhosis diagnosed to have hepatic encephalopathy were enrolled.

Patient's detailed demographics including age, sex, and etiology of liver cirrhosis were recorded after taking written consent. In previous reports, we admitted to the hospital patients who have not had liver encephalopathy. We removed patients who have previously used rifaximine or prophylaxis for any bacterial infection / symptom. Full medical evaluations were administered using different guidelines based on the experience of both patients. Several laboratory tests under lab-technician supervision, i.e. blood, liver, renal function, ultrasound included (abdominal) were performed. We then arranged for all the patients to be divided in two separate groups. Each group contains 40 patients, Group 1 received 200 mg dose of rifaximin twice a daily and group 2 received 550 mg of rifaximin along with lactulose twice a daily. Patients were followed for 6 months. Effectiveness in term of development of hepatic encephalopathy and mortality were examined at the end of treatment. Data was analyzed by SPSS 24.0. Mean±SD was done. Chi-square test was applied to compare the overt hepatic encephalopathy and mortality between low and high dose groups with p-value <0.05 was taken as statistically significant.

RESULTS

There were 22 (55%) male and 18 (45%) female patients in group 1 and in group 2, 20 (50%) patients were male and 20 (50%) were females. No significant difference was observed regarding mean age of patients between both groups 1 and 2 (48.76±11.38 years Vs 49.02±10.44 years). Hepatitis C was the commonest etiology of liver cirrhosis found in 22 (55%) and 21 (52.5%) patients followed by hepatitis B in 12 (30%) and 13 (32.5%) patients and hepatitis B and C in 6 (15%) and 6 (15%) patients in group 1 and 2 respectively (Table 1).

Table 1: Demographic information of the patients

Variable	Group 1	Group 2
Mean age (years)	48.76±11.38	49.02±10.44
Gender		
Male	22 (55%)	20 (50%)
Female	18 (45%)	20 (50%)
Etiology		
Hepatitis C	22 (55%)	21 (52.5%)
Hepatitis B	12 (30%)	13 (32.5%)
Both B&C	6 (15%)	6 (15%)

Table 2: Comparison of overt hepatic encephalopathy between both groups

Overt hepatic encephalopathy	Group 1	Group 2	P-value
Yes	16 (40%)	14 (35%)	0.88
No	24 (60%)	26 (65%)	

Table 3: Comparison of mortality between both groups

Mortality	Group 1	Group 2	P-value
Yes	9 (22.5%)	8 (20%)	0.97
No	31 (77.5%)	32 (80%)	

In group 1, prostosystemic encephalopathy developed in 16 (40%) patients and in group 2 it was developed in 14 (35%) patients, no significant difference was found between both groups with p-value >0.05 (Table 2). During follow-up overall 17 patients were died, 9 (22.5%) in group 1 and 8 (20%) in group 2. There were no any significant difference found between died patients [P = 0.97] (Table 3). Different side effects examined in this study like bloating and abdominal pain in 15(18.8%) patients, nausea/vomiting in 9 (11.25%) patients and headache in 11(13.75%) patients. There was no difference found in high dose as compared to low dose regarding side effects of medication.

DISCUSSION

Symptoms may start and progress, or suddenly, start and progress rapidly in patients suffering from hepatic encephalopathy. Hyperammonemia contributes to altered mental state is the hallmark of liver encephalopathy. Hepatic encephalopathy is demonstrated by a clear history of hepatic failure. Inverse sleep-wake cycles (combination of restless night and heavy diurnal sleep), personality changes, altered perception, bilateral arm-wake tremors (asterixis), agitation and irritability are the most commonly observed signs of hepatic encephalopathic disease.[3,10]

No disparity in effectiveness has been observed in the low dose community rifaximinversus high dose in hepatic encephalopathy prevention. Similarly, in study patients, side effects were mild, mostly associated with GI, which can be easily monitored. The efficacy of rifaximin 100mg/day for more than two years was tested by Muller et al[11] and reported that it is very successful in the prophylaxis of overt hepatic encephalopathy and healthy with no significant side effects. It may be preferred to be used in primary OHE prophylaxis because of lower dosage costs for rifaximin.

Thirty (37.5%) patients developed overt hepatic encephalopathy with rifaximin in our study, which is not optimum when compared to lactulosealone which is already recommended for primary prophylaxis of OHE, routine use of rifaximin as primary prophylactic drug still can't be recommended. Studies demonstrated that low dose of rifaximin for long term use was effective for primary prophylaxis of overt hepatic encephalopathy.[12,13]

In the present study, we found that overall 17 patients were died, 9 (22.5%) in low dose group and 8 (20%) in high dose group. There was no any significant difference found between both groups regarding mortality (p value 0.97). A study conducted by Ali et al[14] reported that no significant difference regarding mortality and adverse outcome between rifaximin and placebo group with p-value >0.05. Some other studies demonstrated that use of rifaximin and other medications showed no significant difference regarding mortality and severe adverse outcomes.[15,16]

This study showed that 52.5% patients were male and 47.5% were female with mean age 47.87±12.74 years. Most common etiology was hepatitis C followed by hepatitis B and both B and C. These results were comparable to many of previous studies.[17,18]

CONCLUSION

The use of rifaximin either low or high dose is not effective to prevent development of protosystemic hepatic encephalopathy. No significant difference was observed in term of development of protosystemic encephalopathy and mortality between low and high dose of rifaximin

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