Original Article

Efficacy of Rifaximin in Treatment of Hepatic Encephalopathy

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Objective: To compare the efficacy of rifaximin vs control group in addition to lactulose for treatment of hepatic encephalopathy with constipat

Methods: A total 100 patients were enrolled in this study. After taking an informed consent the demographic data was collected. Patients were well informed regarding the treatment and its possible effect. The patients were examined for the confirmation of hepatic encephalopathy with constipation. Patients were randomly divided into two groups. Group A received additional rifaximin with lactulose and Group B received only lactulose. The treatment was continued for four months and then patients were observed.

Results: In our study, 18%(n=9) in Group-A and 24%(n=12) in Group-B were between 18-30 years of age while 82%(n=41) in Group-A and 76%(n=38) in Group-B were between 31-60 years of age, mean±sd was calculated as 47.7±10.44 and 46.1±10.77 years respectively. Comparison of efficacy in both groups shows 68%(n=34) in Group-A and 58%(n=29) in Group-B while 32%(n=16) in Group-A and 42%(n=21) in Group-B had no findings of efficacy.

Conclusion: We concluded that the efficacy of rifaximin is significantly better when compared to control group in addition to lactulose for treatment of hepatic encephalopathy with constipation.

Key words: Hepatic encephalopathy, management, rifaximin, efficacy

Introduction

Hepatic encephalopathy is a syndrome observed in patients with cirrhosis. Hepatic encephalopathy is defined as a spectrum of neuropsychiatric abnormalities in patients with liver dysfunction, after exclusion of other known brain disease and metabolic cause. Hepatic encephalopathy is characterized by personality changes, intellectual impairment, and a depressed level of consciousness. An important prerequisite for the syndrome is diversion of portal blood into the systemic circulation through portosystemic collateral vessels.[1] Subtle signs of hepatic encephalopathy are observed in nearly 70% of patients with cirrhosis. Symptoms may be debilitating in a significant number of patients. Overt hepatic encephalopathy occurs in about 30-45% of patients with cirrhosis.[2] The clinical signs and symptoms of hepatic encephalopathy may range from mild cognitive impairment to profound coma. These include forgetfulness, alteration in sleep-wake cycle, changes in personality and emotions, hyperreflexia and drowsiness. In more severe cases disorientation, constructional apraxia, asterixis, seizures and eventually coma may develop. It is very important to exclude other causes of altered mental status or encephalopathy in suspected patients for appropriate management of HE.[3] For 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. 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.[4] The rationale of this study is to determine the importance of additional rifaximin with lactulose for the treatment of hepatic encephalopathy in local population. The results of this study will help us to take decisions to advice the patients this treatment for hepatic encephalopathy.

Method

A total 100 patients were enrolled in this study. After taking an informed consent the demographic data was collected. Patients were well informed regarding the treatment and their effect in a language they can understand best. If patient is not conscious than his attendant was asked for permission. The patients were examined for the confirmation of hepatic encephalopathy with constipation. Patients were randomly divided into two groups. Group A received additional rifaximin with lactulose and Group B received only lactulose. The treatment was continued for four months and then patients were observed.

Results

A total of 100 cases (50 in each group) were

enrolled to compare the efficacy of rifaximin vs control group in addition to lactulose for treatment of hepatic encephalopathy with constipation. Patients were distributed according to age, it was showing that 18%(n=9) in Group-A and 24%(n=12) in Group-B were between 18-30 years of age while 82%(n=41) in Group-A and 76%(n=38) in Group-B were between 31-60 years of age, mean+sd was calculated as 47.7±10.44 and 46.1±10.77 years respectively. Duration of constipation was recorded as 38%(n=19) in Group-A and 32%(n=16) in Group-B had <3 days of constipation while 62%(n=31) in Group-A and 68%(n=34) in Group-B had >3 days of constipation. (**Table 1**)

Table-1: Demographics of the women

Duration of Constipation (in days)	Group- B (n=50)		Group- B (n=50)	
	No of Patients	%	No of Patients	%
<3	19	38	16	32
> 3	31	62	34	68
Total	50	100	50	68

Frequency of grade of encephalopathy according to West Haven criteria was recorded and showing that 28%(n=14) in Group-A and 32%(n=16) in Group-B had grade 2, 42%(n=21) in Group-A and 36%(n=18) in Group-B had grade 3 while 30%(n=15) in Group-A and 32%(n=16) in Group-B had grade 4. (**Table No. 2)**

Table-1: Demographics of the women

Grade	Group- B (n=50)		Group- B (n=50)	
	No of Patients	%	No of Patients	%
1	-	-	-	-
2	14	28	16	32
3	21	42	18	36
4	15	30	16	32
Total	**50**	**100**	**50**	**100**

Comparison of efficacy in both groups shows 82%(n=41) in Group-A and 58%(n=29) in Group-B while 18%(n=19) in Group-A and 42%(n=21) in Group-B had no findings of efficacy, p value was calculated as 0.008. (**Table No. 3**)

Table-1: Demographics of the women

Efficacy	Group- B (n=50)		Group- B (n=50)	
	No of Patients	%	No of Patients	%
Yes	41	82	29	58
No	09	18	21	32
Total	50	100	50	100

P value=0.00

Discussion

Hepatic encephalopathy is a challenging complication in patients with advanced liver disease. Diagnosis of hepatic encephalopathy is currently based on specific tests evaluating the neuropsychiatric state of patients and their quality of life; the severity of hepatic encephalopathy is measured by the West Haven criteria. Treatment of hepatic encephalopathy consists of pharmacological and corrective measures, as well as nutritional interventions. Rifaximin received approval for the treatment of hepatic encephalopathy in 2010 because of its few side effects and pharmacological benefits.

We planned this study with the view to determine the importance of additional rifaximin with lactulose for the treatment of hepatic encephalopathy. There is no local study available for this topic that's why we conducted this study. In previous studies, episodes of HE were reported in 22.1% of patients in the rifaximin group and in 45.9% of patients in the placebo group. The hazard ratio for the risk of a breakthrough episode in the rifaximin group was 0.42 (95% CI: 0.28-0.64), accounting for a relative risk reduction of 58% with rifaximin compared with placebo during the 6 months follow-up,[5] however, it supports our study results.

A trial comparing rifaximin with placebo found that the active therapy significantly improved only asterixis, whilst PSE index, mental status and intellectual function similarly improved in both groups.[6] In another placebo-controlled trial, rifaximin was claimed to be superior compared to placebo.[7] A recent randomized trial compared the efficacy of 8 week rifaximin therapy in improving health-related quality of life (HRQOL) in minimal HE cirrhotics compared with placebo.[8] Rifaximin was found to be significantly associated with an improvement of HRQOL. However, data of this study have been criticized, an imbalance between the patients randomized in the two arms being present.[9] In detail, patients randomized to rifaximin appeared to have most of the baseline scores (social interactions, emotional behavior, ambulation, mobility, body care and movements) at higher levels compared to the placebo group, suggesting a worse score at baseline in this group. Despite the rifaximin group showing a significant improvement of scores at 8 wk, the final values would not appear different from the final values observed in the placebo group.[8] Therefore, it cannot be excluded that the higher efficacy of

rifaximin was related to the poorer baseline conditions rather than to a real efficacy of the drug.[9] Consequently, this data should be considered with caution.

Rifaximin has been proved to be safe in healthy subjects. However, liver cirrhosis significantly affects the pharmacokinetics of this drug, with systemic absorption markedly increased in these patients compared to controls. Indeed, plasma concentrations as high as 10 ng/mL have been observed in cirrhotics, with levels being even higher in those patients with Child-Pugh C disease, compared to only 1 ng/mL in controls.[10] This could be a cause for concern, particularly when a daily, long-life therapy is proposed for chronic disorders, such as HE recurrence prevention.[7] Therefore, a note for caution should be considered before suggesting long-term therapy with rifaximin for HE prevention in cirrhotics and further studies are warranted to assess its actual safety.

However, according to the results of our study, we found a significant difference between the two groups. As our study is primary in our setup, it needs to be validated through some-other trials.

Conclusion

We concluded that the efficacy of rifaximin is significantly better when compared to control group in addition to lactulose for treatment of hepatic encephalopathy with constipation.

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