ORIGINAL ARTICLE

Lactulose alone versus Lactulose + Rifaximin for the management of Hepatic Encephalopathy

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ABSTRACT

Aim: To compare the of lactulose plus rifaximin with efficacy of lactulose alone in the management of hepatic encephalopathy (HE).

Methods: All the patients presenting with hepatic encephalopathy secondary to decompensated chronic liver disease (DCLD) were enrolled in the study. Patients were randomized into two groups; A and B, via lottery method. Those in group A received lactulose 30 ml thrice daily whilst those in group B were given lactulose 30 ml thrice daily plus rifaximin 550 mg twice daily.Patients were followed up on day to day basis for a period of 3 days. Primary outcome was efficacy; defined as the the percentage of patients who underwent reversal of HE. All the data was recorded on a pre-designed proforma and analyzed by SPSS version 23.0. Chi square test was applied to compare the efficacy taking p value < 0.05 as statistically significant.

Results: The two groups were comparable in terms of baseline characteristics such as mean age (p value = 0.63), gender (p value = 0.71), child class (p value = 0.74) and grade of HE (p value = 0.66). Lactulose alone (Group A) was found to be efficacious in 53.3% (32 out of 60) of the cases whilst 83.3% (50 out of 60) of the patients achieved reversal of HE in group B (Lactulose + Rifaximin group). The difference seen was statistically significant (p value = 0.0004).

Conclusion: The combination of Rifaximin and lactulose was superior to lactulose alone in achieving reversal of hepatic encephalopathy.

Keywords: Hepatic encephalopathy (HE), Decompensated chronic liver disease (DCLD), Hepatitis C

INTRODUCTION

Hepatic encephalopathy (HE) is one of the commonest complications of chronic liver disease (CLD). Symptoms of HE may be present in upto 30-45% of the patients with liver cirrhosis[1]. Pakistan has a very high prevalence of CLD secondary to the huge burden of hepatitis B and C in the country[2]. In fact, Pakistan has the second highest prevalence of hepatitis C in the world estimated to be around 6.8%[3]. Moreover, Pakistan is home to about 7-9 million carriers of hepatitis B virus (HBV)[4]. This explains the huge burden of chronic liver disease in Pakistan.

Hepatic encephalopathy is characterized by a constellation of neuropsychiatric symptoms which range from mild behavioral changes and drowsiness to coma[5]. The pathogenesis involves increased levels of ammonia secondary to ineffective urea cycle in the liver. The ammonia is then removed as glutamine in the astrocytes leading to astrocyte swelling and brain edema[6]. Various precipitating factors have been identified. These include gastrointestinal bleed, infection, electrolyte disturbances, constipation, high protein intake and sedatives such as benzodiazepines.

Hepatic encephalopathy, if not managed timely, is associated with increased mortality especially with higher grades of HE[7]. Drugs aimed at reversing HE work primarily by lower ammonia levels. Current treatment guidelines recommend using lactulose for the initial management of HE. It works by reducing intestinal ammonia production. Moreover, it relieves constipation, one of the major precipitating factor of HE. Recently, clinical trials have shown that rifaximin is as effective as lactulose in management of HE.8,9 Moreover, multiple studies have been done comparing lactulose + rifaximin versus lactulose alone for treatment of HE. There are mixed findings regarding this. Sharma et al[9] showed that combination of lactulose plus rifaximin was more effective than lactulose alone in the reversal of overt HE (p < 0.004). A possible explanation for this might be that since rifaximin and lactulose have different mechanisms of action; they act synergistically in combination and hence show better response in treating HE. Ahire et al[10] showed no significant difference between the two groups in terms of efficacy (p=0.3251). A recent local study by Butt et al[11] echoed similar findings (p=0.276). These conflicting results coupled with the scarce local literature available on this topic prompted us to conduct this study.

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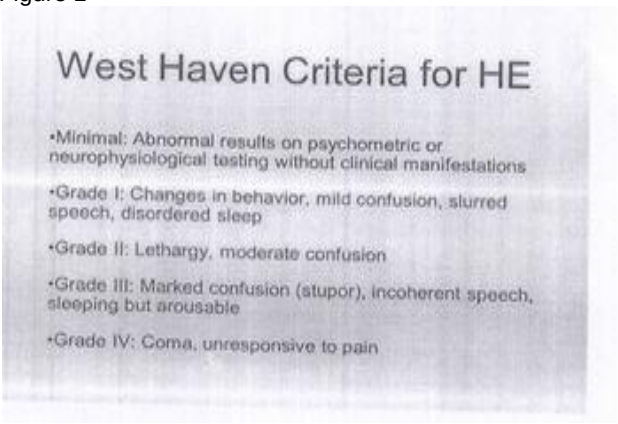
MATERIALS AND METHODS

This non blinded randomized control trial was conducted in medical department of dhq teaching hospital sheikhupura from janurary 2017 to august 2017. The sample size was calculated using openepi calculator with the statistical assumptions of 5% alpha error and 95% confidence interval taking proportion of patients showing reversal of HE in combination group to be 76% and proportion of patients showing reversal of HE in lactulose alone group to be 50.8% and comes out to be at least 60 patients in each group for this study.Ethical approval was taken from institutional review board. All the patients presenting with hepatic encephalopathy secondary to decompensated chronic liver disease (DCLD) were enrolled in the study. Patients with encephalopathy secondary to other causes such as renal failure, electrolyte disturbances, sedative overdose, cerebrovascular accidents, metabolic encephalopathy and acute fulminant hepatic failure were

excluded from the study. Informed consent was taken. Detailed clinical history and physical examination was done in each case. HE was graded according to west haven criteria and precipitating factor identified. Patients were randomized into two groups; A and B, via lottery method. Those in group A received lactulose 30 ml thrice daily whilst those in group B were given lactulose 30 ml thrice daily plus rifaximin 550 mg twice daily.Patients were followed up on day to day basis for a period of 3 days. Primary outcome was efficacy; defined as the the percentage of patients who underwent reversal of HE. Reversal of HE was defined as from recovery from grade-IV/grade III to grade-I or below after 3 days of treatment.

Figure 1



All the data was recorded on a pre-designed proforma and analyzed by SPSS version 23.0. Mean and standard deviation was calculated for all quantitative variables like age etc. Frequency and percentage was calculated for all qualitative variables like efficacy, grades of HE, precipitating factors of HE etc. Chi square test was applied to compare the efficacy taking p value < 0.05 as statistically significant.

RESULTS

One hundred and twenty patients took part in this randomized controlled trial comprising of 66 males and 54 females. Overall mean age of the patients was 53.8 ± 10.1 years (Table 1). Lactulose alone (Group A) was found to be efficacious in 53.3% (32 out of 60) of the cases whilst 83.3% (50 out of 60) of the patients achieved reversal of HE in group B (Lactulose + Rifaximin group). The difference seen was statistically significant (p value = 0.0004) (Table 2).Etiology of DCLD was found to be hepatitis C in 90 (75%), hepatitis B in 16(13.3%) and other causes in 14 (11.7%) cases. 3 patients were in child class A (2.5%), 22 (18.3%) patients were in child class B and 95 (79.2%) were in child class C. The two groups were comparable in terms of baseline characteristics such as mean age (p value = 0.63), gender (p value = 0.71), child class (p value = 0.74) and grade of HE (p value = 0.66) (Table 1).

Table 1: Baseline characteristics

	Group A (n=60)	Group B (n=60)	Overall (n=120)	p value
Mean age ± SD in years	53.2 ± 10.6	54.1 ± 9.8	53.8 ± 10.1	0.63
Male / Females	32 / 28	34 / 26	66 / 54	0.71
Child class A / B / C	1 / 10 / 49	2 / 12 / 46	3 / 22 / 95	0.74
West haven Grade I / II / III / IV	4 / 10 / 26 / 20	2 / 12 / 30 / 16	6 / 22 / 56 / 36	0.66

Table 2: Comparison of efficacy of the two groups in reversal of hepatic encephalopathy (HE)

	Group A	Group B
Reversal	32 (53.3%)	50 (83.3%)
No reversal	28 (46.7%)	10(16.7%)

P value=0.0004

DISCUSSION

Hepatic encephalopathy is a potentially serious complication of decompensated chronic liver disease. It is associated with increased mortality if not managed appropriately. HE primarily results from increased ammonia levels in the blood secondary to liver's inability to detoxify. Majority of treatment modalities aim at lowering the ammonia level.

We conducted this study with the objective of comparing efficacy of lactulose plus rifaximin with efficacy of using lactulose alone for treatment of HE. Our study concluded that the combination of rifaximin and lactulose was significantly more efficacious than lactulose alone in achieving reversal of HE (p value 0.0004).Reversal of HE was seen in 53.3% of patients in lactulose alone group compared with 83.3% of the patients in the combination group. Similar findings were echoed by Sharma et al9 who showed that reversal of HE was seen in 50.8% of patients in lactulose alone group compared with 76% of patients in the combination group (p value <0.004). However other studies found no significant difference in efficacy amongst the two groups[10,11]. The two groups were comparable in terms of baseline characteristics in our study as was the case with Sharma et al's9 study. Mean age of patients seen in our study was 53.8 ± 10.1 years which was higher compared to that observed by Sharma et al[9] (39.4 ± 9.6 years). However it was comparable to the mean age reported by Butt et al[11]. Our study reported hepatitis C the major cause of DCLD seen in 75% of the cases whereas Sharma et al9 reported alcoholism as the leading cause of DCLD. This difference is understandable considering the high prevalence of HCV in Pakistan. Also, being an islamic republic, alcoholism has never been a major problem in Pakistan. Similar trend was observed by Haq et al[12] who reported HCV to be responsible for upto 86.9% of the

cases. Our study showed that majority of the patients were child class C (79.2%). We also reported that bulk of the patients were having grade III (46.7%) or grade IV (30%) encephalopathy. Similar trend was noticed by Haq et al12 who also showed that most patients were either child class C(68.7%) or had grade III (31.8) or grade IV (48.12%).

There were certain limitations to our study with the most important being the non blinded study design. Ideally, it should have been a double blind RCT.This would have significantly removed the element of bias. Moreover potential effect modifiers and confounders (gender, grades of HE) were not controlled. Ideally stratification should have been done and post stratification chi square test applied to control confounders.

CONCLUSION

Rifaximin and lactulose combination is superior to lactulose alone in achieving reversal of hepatic encephalopathy. However, large multicenter double blinded RCTs are warranted in the near future to confirm these preliminary findings.

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