ORIGINAL ARTICLE

Decrease in Porto-systemic Encephalopathy (PSE) Scores in patients with Hepatic encephalopathy on low dose Rifaximin

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ABSTRACT

Background: Cirrhosis of liver is a frequent cause of admissions in hospitals due to its complications particularly hepatic encephalopathy (HE) and gastro intestinal bleed. Mortality of inpatients with HE remained relatively stable and high in the previous years. The antibiotic Rifaximin is a relatively new drug introduced in the prevention of hepatic encephalopathy.

Aim: To determine the mean decrease in PSE score in patient with hepatic encephalopathy in dose of 600mg per day Rifaximin in three divided doses.

Methods & Results: There were 300 patients in total. Males were 164/300 (54.7%) while females were 136/300 (45.3%). Mean age of the patients was 50.07 + 11.59 years. There were 36/300 (12.7%) with Child's class A, 126/300 (42%) in child's class B while there were 136/300 (45.3%) with Child's class C. Mean PSE score (Conn's score) before the start of treatment was 3.17 + 0.721 while mean PSE score after completion of treatment was 1.79 + 0.879 with P-Value < 0.001. The improvement in PSE score was found to be statistically significant among males and females, in various age groups and in patients with various classes of Child Pugh score.

Conclusion: Rifaximin is an effective treatment option in patients with cirrhosis of liver who have hepatic encephalopathy which results in significant improvement in PSE score (Conn s' score) among patients with hepatic encephalopathy.

Keywords: Encephalopathy, Rifaximin, gastrointestinal bleed

INTRODUCTION

Cirrhosis is a consequence of chronic liver disease characterized by replacement of liver tissue by fibrosis, scar tissue and regenerative nodules leading to loss of liver function[1]. Cirrhosis has many causes. In the United States, the most common causes are chronic alcoholism and hepatitis[2]. In Pakistan prevalence of hepatitis C (HCV) is 4.9% and hepatitis B (HBV) is 2.5%[3]. Subtle signs of HE are seen in about 70% of patients with cirrhosis and approximately 30% of patients with end stage liver disease experience significant HE requiring hospitalization[4]. Mortality of inpatients with HE remained relatively stable at 14.13% to15.61%[5]. Constipation, gastrointestinal bleeding and infections are the most common precipitating factors of HE in our patients[6,7]. In some cases, a person with hepatic encephalopathy may become unresponsive and slip into a coma8and there is an increased risk of death[9].

In general the oral antibiotics neomycin, paromomycin, vancomycin and metronidazole have been effectively used with or without lactulose to reduce ammonia producing enteric bacteria in patients with hepatic encephalopathy[10].

Rifaximin is a new drug introduced for prevention of hepatic encephalopathy. Rifaximin is a minimally absorbed oral antimicrobial agent that is concentrated in the gastrointestinal tract has broad spectrum in vitro activity against gram positive, gram negative, aerobic, anaerobic enteric bacteria and has a low risk of inducing bacterial resistance[11]. It is used in eradicating SIBO[12] (small intestinal bacterial over growth), relief of IBS symptoms; bloating, abdominal pain, loose or watery stools13 and diminishes neutropenia following potentially lethal whole-body radiation[14]. Rifaximin appears to be at least as effective as other conventional oral agents for the prevention of PSE with a better safety profile[15,16,17,18]. It is approved by FDA for the prevention of PSE in a dose 550mg per oral twice daily. The risk of experiencing a breakthrough overt PSE episode was reduced by 58% in Rifaximin-treated subjects compared with placebo (primary endpoint)[16]. The drug is costly and considering its long term use many patients in our country may find difficult to comply. In another study the PSE score was 37.8±11.4 at day 1 while after 7 days was 31.9±16.9 with a change of -6.4±13.7 in a dose of 600mg per oral per day.19

The objective of the study was to determine the mean decrease in PSE score in patient with hepatic encephalopathy in dose of 600mg per day Rifaximin in three divided doses.

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MATERIALS AND METHODS

There were total 300 patients included in our study from July 2016 to December 2017(Six months) , in the department of Gastroenterology and Hepatology in Saira Meraj Hospital ,Lahore, Pakistan. Quasi-experimental Study. Sample size estimated using 95% confidence level 5% margin of error with and expected reduction of PSE score 6.4±13.7 is 300. Non probability purposive sampling technique was used.

Inclusion criteria: Patients of both gender i.e. male and female ,Age of at least 18 years, At least two episodes of overt hepatic encephalopathy (Conn score, ≥2) associated with hepatic cirrhosis during the previous 6 months, A score of 25 or less on the Model for End-Stage Liver Disease (MELD) scale.

Study protocol: Total 300 patients with cirrhosis who fulfilled the inclusion criteria were included in the study from the Indoor patient Department of Gastroenterology Hepatology Saira Meraj Hospital Lahore. Informed consent was taken in the language the respondent or its attendant could understand the best. Baseline PSE score was recorded. Patients received low dose of Rifaximin 600mg per day in three divided doses per oral for six months. PSE score was again recorded after six month of treatment compliance. PSE was diagnosed by West Haven Criteria (annexed). All the data was entered in a well designed Performa.

Statistical analysis: The data was entered and analyzed by using SPSS 15.0. Quantitative variables like age of patient and decrease in PSE were presented as mean and standard deviation. Qualitative variables like sex of patient, child's class were expressed in terms of frequency and percentages. Data was stratified for Childs' class to address effect modifiers.

RESULTS

There were 300 patients in total. Males were 164/300 (54.7%) while females were 136/300 (45.3%). Mean age of the patients was 50.07 + 11.59 years ranging from a minimum of 19 to a maximum of 67 years. There were 36/300 (12.7%) with Child's class A, 126/300 (42%) in Child's class B while there were 136/300 (45.3%) with Child's class C. Mean Conn's score (PSE score) before the start of treatment was 3.17 + 0.721 ranging from a minimum of 2 to a maximum of 4 while mean PSE score after completion of treatment was 1.79 + 0.879 ranging from a minimum of 1 to a maximum of 4. The t-value was 14.93508 and the P-Value was < 0.001 (Table 1, Fig. 1,2,3).

Table 1: Characteristics of the patient population (n=300)

Male	164/300 (54.7%)
Female	136/300 (45.3%)
Mean age	50.07 + 11.59
Child's class	
A	36/300 (12.7%)
B	126/300 (42%)
C	136/300 (45.3%)
Conn's PSE score	
Start of treatment	3.17 + 0.721 0.001
After treatment	1.79 + 0.879

Table 2 : West Haven Criteria for Semi quantitative Grading of Mental State West Haven Criteria for Semi quantitative Grading of Mental State
Grade 1 Trivial lack of awareness
Euphoria or anxiety
Shortened attention span
Impaired performance of addition
Grade 2 Lethargy or apathy
Minimal disorientation for time or place
Subtle personality change
Inappropriate behavior
Impaired performance of subtraction
Grade 3 Somnolence to semi stupor, but responsive to verbal stimuli
Confusion
Gross disorientation
Grade 4 Coma (unresponsive to verbal or noxious stimuli)

When the effect of gender was noted it was found that there were 164 male patients with mean age of 49.30+11.23 years ranging from a minimum of 19 to a maximum of 67 years. The mean PSE score (Conn's score) before treatment was 3.17+0.717 and after treatment it was 1.78+0.889 (P-value <0.01). Among 136 females the mean age of the patients was 51+12.03 years ranging from a minimum of 20 to a maximum of 66 years. Mean PSE score (Conn's score) before and after treatment was 3.18+0.732 and 1.94 + 0.896 respectively (P-value < 0.01) (Table 3, Figure 4).

Table 3: Comparison of various patient characteristics among males and females

	Males (n = 164)	Females (n = 136)	p-value
Mean age	49.30 + 11.23	51 + 12.03	
Child's class			
A			
B			
C			
Conn's score			
Start of treatment	3.17 + 0.717	3.18 + 0.732	0.01
After treatment	1.78 + 0.889	1.94 + 0.896	

When the effect of age was noted it was found that in patients with age group < 45 years there were 62/98 (63.26%) males and 36/98(36.73%) females with a mean Conn's score before treatment of 3.0 + 0.707 and after treatment of 1.86 + 0.890 (p-value < 0.01). In age group > 45 years there were 202 patients with 102/202 (50.49%) males and 100/202 (49.5%) females. Mean Conn's score before treatment was 3.26 + 0.716 and after treatment it was 2.01 + 0.843 (p-value <0.01) (Table 4, Figure 5).

Conn's score P-value
Start of treatment After treatment
Age < 45 3.0 + 0.707 1.86 + 0.890 0.01
Age > 45 3.26 + 0.716 2.01 + 0.843 0.01

When the effect of Child`s score was noted it was found that in Child class A there were 36 patients with 16/36 (42.1%) males and 22/36 (57.9%) females. Mean age of the patients was 49.42 + 11.92 years. Mean Conn's score before and after treatment were found out to be 3.05 + 0.780 and 2 + 0.943 (p-value < 0.01). In patients falling in Child Class B there were 126 patients with 76/126 (60.3%) males and 50/126 (39.7%) females. Mean age of the patients was 50.89 + 10.62 years. Conn's score was found to be 3.11 + 0.76 and 1.97 + 0.897 before and after treatment respectively (p-value < 0.01). In patients falling in Child`s Class C there were 136 patients with 72/136 (52.9%) males and 64/136 (47.1%) females. Mean age of the patients was 49.50 + 12.46 years. Conn's score was found to be 3.26 + 0.661 and 1.94+0.808 before and after treatment respectively (p-value < 0.01) (Table 5 , Figure 6).

Table 5: Comparison of mean Conn's score before and after treatment among patients with different Child Pugh class.

Conn's score P-value
Start of treatment After treatment
Child`s Class A 3.05 + 0.780 2 + 0.943 0.001
Child`s Class B 3.11 + 0.764 1.73+0.897 0.001
Child`s Class C 3.26 + 0.661 1.75+0.853 0.001

Figure 6: Comparison of mean Conn's score before and after treatment among patients with different Child pugh class.

Table 1: Characteristics of the patient population (n=300)

Males		164/300 (54.7%)
Females		136/300 (45.3%)
Mean age		50.07 + 11.59
Child's class	A	36/300 (12.7%)
	B	126/300 (42%)
	C	136/300 (45.3%)
Conn's PSE score	Start of treatment	3.17 + 0.721
	After treatment	1.79 + 0.879

P Value 0.001

Table 2 : West Haven Criteria for Semi quantitative Grading of Mental State

	West Haven Criteria for Semi quantitative Grading of Mental State
Grade 1	Trivial lack of awareness Euphoria or anxiety Shortened attention span Impaired performance of addition
Grade 2	Lethargy or apathy Minimal disorientation for time or place Subtle personality change Inappropriate behavior Impaired performance of subtraction
Grade 3	Somnolence to semi stupor, but responsive to verbal stimuli Confusion Gross disorientation
Grade 4	Coma (unresponsive to verbal or noxious stimuli)

Fig. 1: Frequency of gender distribution in the patient population.

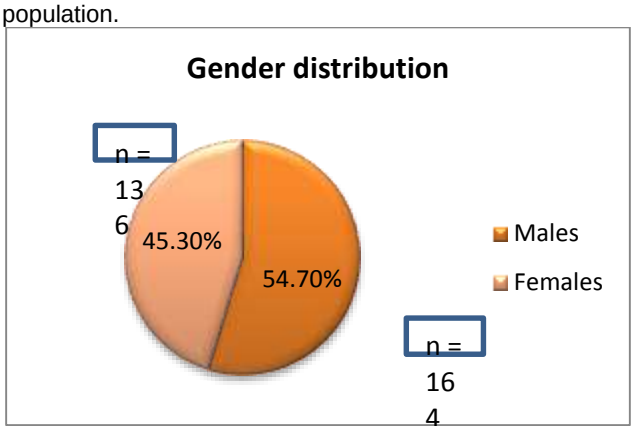


Fig. 2: Frequency of patients in various classes of Child's score

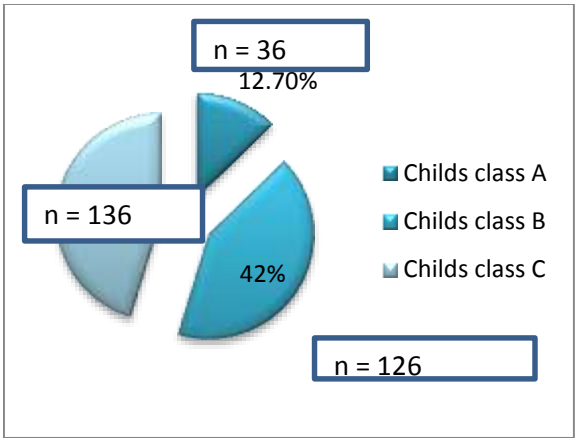


Fig. 3: Comparison of mean decrease in Conn's score after treatment with Rifaxamin

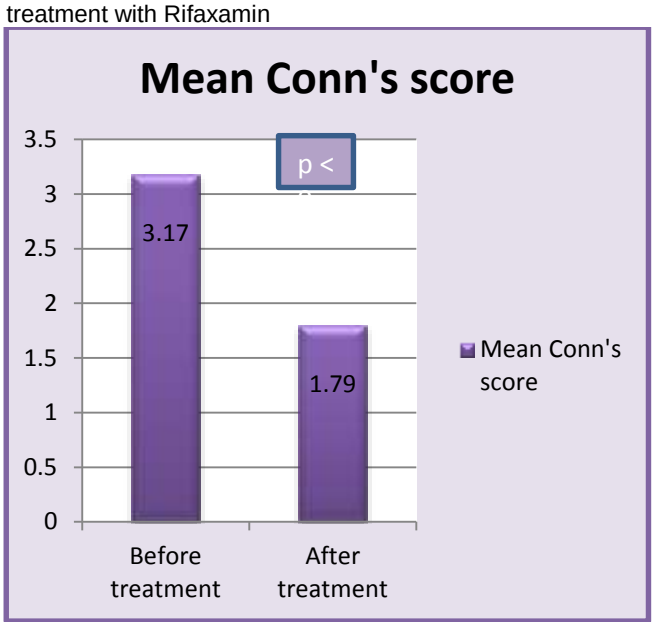


Table 3: Comparison of various patient characteristics among males and females

		Males (n = 164)	Females (n = 136)
Mean age		49.30 + 11.23	51 + 12.03
Conn's score	Start of treatment	3.17 + 0.717	3.18 + 0.732
	After treatment	1.78 + 0.889	1.94 + 0.896

P value=0.01

Fig. 4: Comparison of mean Conn's score before and after treatment with Rifaxamin among males and females.

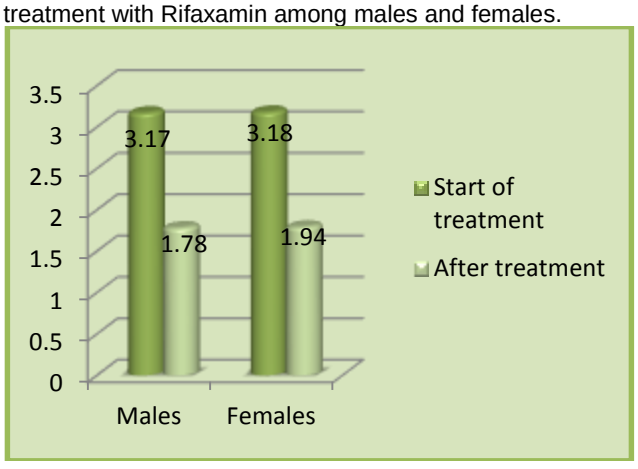


Table 4: Comparison of mean Conn's score before and after treatment among patients with different age groups.

	Conn's score		P-value
	Start of treatment	**After treatment**	
Age < 45	3.0 + 0.707	1.86 + 0.890	0.01
Age > 45	3.26 + 0.716	2.01 + 0.843	0.01

Fig. 5: Comparison of mean Conn's score before and after treatment among patients with different age groups.

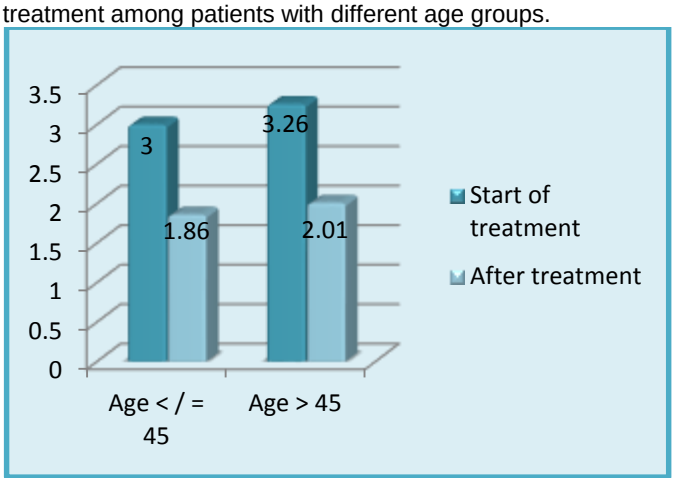
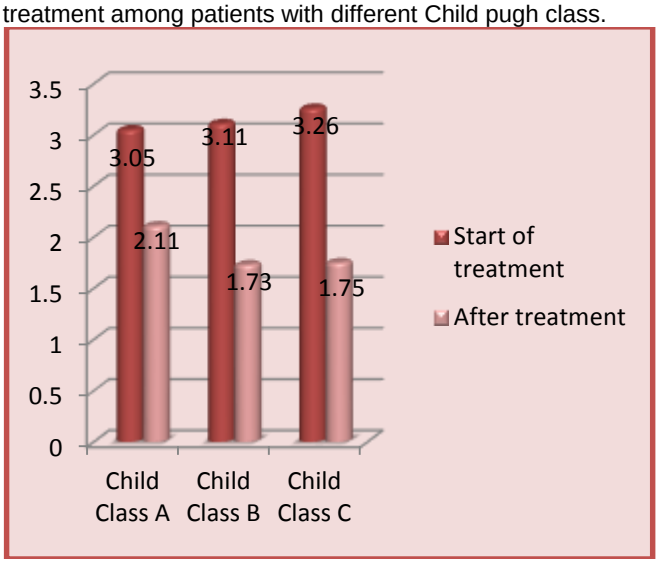


Table 5: Comparison of mean Conn's score before and after treatment among patients with different Child Pugh class.

	Conn's score		P-value
	Start of treatment	**After treatment**	
Child`s Class A	3.05 ± 0.780	2 ± 0.943	0.001
Child`s Class B	3.11 ± 0.764	1.73 ± 0.897	0.001
Child`s Class C	3.26 ± 0.661	1.75 ± 0.853	0.001

Fig. 6: Comparison of mean Conn's score before and after treatment among patients with different Child pugh class.



DISCUSSION

Estimates suggest approximately 5.5 million people in the United States suffer from cirrhosis of the liver and 30-45% of those experience symptoms of Hepatic encephalopathy (HE).20 21

Recently, rifaximin has been indicated for use in reducing the risk of recurrent HE at a dose of 550 mg twice daily.22Results indicated improvement in

patients and found rifaximin was best tolerated at the 1200 mg per day dose.23In 1995, the efficacy and safety of rifaximin was evaluated in 55 patients with grades 1-3 hepatic encephalopathy.24 Another group conducted a dose-ranging trial of rifaximin for treatment of hepatic encephalopathy.25An open-label trial evaluated 26 patients with cirrhosis and hepatic encephalopathy who did not respond to or experienced severe adverse events during treatment with therapeutic doses of lactulose.26 In 1991, results compared the safety of rifaximin.27In another study hepatic encephalopathy was treated withrifaximin 28 .In 1997, results from a randomized, doubleblind, multicenter trial of 60 patients with grade 1 or 2 hepatic encephalopathy were published.29

In a number of trials, the efficacy of rifaximin was compared with nonabsorbable disaccharides.30-34 Another group carried out a multicenter trial in 136 patients with cirrhosis and grade 1 hepatic encephalopathy.31 A double-blind, double-dummy study was conducted in 40 patients with cirrhosis and grades 1-3 hepatic encephalopathy.32 A controlled trial that evaluated the efficacy and safety of rifaximin compared withlactulose in patients with grade 1-3 acute or recurrent hepatic encephalopathy.33 In a randomized efficacy and safety trial, rifaximin was compared with lactulose in patients with grades 1-3 episodic hepatic encephalopathy.34

In our study there were 300 patients in total with a male predominance 164 (54.7%) while females were 136 (45.3%). Mean age of the patients was 50.07 + 11.59 years which was reflective of the fact that cirrhosis of the liver is more common among elderly patients.34 There were also a number of limitations of our study. It was not a randomized controlled trial and we included a smaller sample size due to lack of resources and limited duration of study. A larger study with a randomized controlled design and detailed assessment including laboratory parameters as well as studies documenting electrophysiological status needs to be conducted to further confirm and delineate the beneficial effects of Rifaximin in the treatment and prevention of hepatic encephalopathy.

CONCLUSION

Rifaximin is an effective treatment option in patients with cirrhosis of liver who have hepatic encephalopathy. It results in significant improvement in Conn's score and PSE score among patients with hepatic encephalopathy and therefore it should be routinely prescribed in these patients to hasten recovery and improve the outcome.

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