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Original Research Article

COMPARISON OF 550MG/DAY VERSES 1100 MG/DAY RIFAXIMIN IN SECONDARY PREVENTION OF BOTH COVERT AND OVERT HEPATIC ENCEPHALOPATHY

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ABSTRACT

Background: *Hepatic encephalopathy (HE) is a serious complication of liver cirrhosis, presenting in covert and overt forms, and often recurs after initial treatment. Rifaximin, a non-absorbable antibiotic, is widely used for secondary prevention, but the optimal dose for preventing HE recurrence remains uncertain.* ***Objective:*** *To compare the frequency of recurrence of both covert and overt hepatic encephalopathy in patient taking rifaximin at 550mg/day verses 1100mg/day.* ***Study Design:*** *Randomized, controlled, comparative study.* ***Setting:*** *Department of Medicine, Sheikh Zayed Hospital, Rahim Yar Khan, Pakistan.* ***Duration of Study:*** *Six months, from September 6, 2024, to March 6, 2025.* ***Methods:*** *A total of 160 patients diagnosed with either covert or overt HE were enrolled and randomized into two treatment groups via block randomization. Group A received 550 mg/day rifaximin, and Group B received 1100 mg/day. The primary outcome was the frequency of HE recurrence over the study period. Statistical analysis was performed using SPSS version 26. Chi-square test was applied to compare recurrence rates between groups, with $p < 0.05$ considered statistically significant.* ***Results:*** *In Group A, 47.5% of patients experienced recurrence of HE, compared to 43.8% in Group B. The difference in recurrence rates between the two groups was not statistically significant ($p = 0.63$).* ***Conclusion:*** *There was no significant difference in the efficacy of 550 mg/day versus 1100 mg/day rifaximin in preventing HE recurrence. Given the comparable outcomes, the standard 550 mg/day dose remains the preferred regimen for secondary prevention of hepatic encephalopathy due to its effectiveness and potential cost-benefit advantage.*

Keywords: Hepatic Encephalopathy, Rifaximin, Covert HE, Overt HE, Secondary Prevention, Recurrence, Cirrhosis

INTRODUCTION

Hepatic encephalopathy (HE) significantly contributes to the frequency of hospital admissions within this group and significantly impacts the health-related quality of life of both patients and caregivers (1). A notable increase in mortality rates is evident in patients experiencing acute-on-chronic liver failure (2). HE can arise spontaneously or as a result of various precipitating conditions such as infection, dehydration, gastrointestinal bleeding, constipation, high dietary protein intake, hypovolemia, shock, hypokalaemia, or the use of medications like opiates as well as benzodiazepines (3, 4). A key aspect of the pathophysiology of HE is hyperammonemia, which arises from a raised nitrogenous load originating in the gastrointestinal tract and decreased urea synthesis. This is attributed to portal-systemic shunting and a reduction in hepatic urea synthesis (5, 6).

Under normal conditions, the brain and skeletal muscle do not remove or produce ammonium; however, during hyperammonemia, they can capture ammonium and discharge glutamine. Ammonia is generated through the bacterial breakdown of amines, amino acids, purines, and urea, in addition to the activity of enterocytic glutaminase that converts glutamine into glutamate along with ammonia (7, 8). A study based on data from the population estimated that around 44% of individuals who developed cirrhosis could develop hepatic encephalopathy over 5 years (9). A separate study with more than 9000 individuals newly diagnosed with cirrhosis showed that approximately one-third presented with decompensated cirrhosis, and among these individuals, 51% developed hepatic encephalopathy (10).

Rifaximin is an oral antimicrobial agent that has little absorption. This compound is derived from rifamycin and exhibits a broad spectrum of activity against gram-positive, gram-negative, and anaerobic enteric bacteria, while also providing a low risk for inducing bacterial resistance. A study indicated that the combination of Rifaximin as well as lactulose demonstrates greater efficacy in preventing the recurrence of HE (11). In a different study, the observed percentage of patients with CHE reversal was implicitly higher in low-dose (41.67%, 5/12) and high-dose (57.14%, 8/14) groups as compared to the control group (7.14%, 1/14) at 8 weeks (12).

This study aims to compare different doses of rifaximin in secondary prevention of Hepatic Encephalopathy. It will help the health practitioner choose the best treatment option to avoid further complications and the severity of the disease. As high doses are cost-effective, clinical Practitioners should decide on the best treatment option.

METHODOLOGY

The study was conducted as a randomized controlled trial in the Department of Medicine at Sheikh Zayed Hospital Rahim Yar Khan 06-September-2024 to 06-March-2025. One hundred and sixty patients diagnosed with either covert or overt hepatic encephalopathy were recruited using non-probability consecutive sampling. WHO calculator was utilized for sample size calculation, considering a 95% confidence level, 6% absolute precision, and anticipated population proportions derived from a prior study (41.67% vs 57.14%) (12).

Participants were randomly assigned to two groups: Group A received 550 mg of rifaximin daily, while Group B received 1100 mg daily. Patients aged 18 to 70 years with a confirmed diagnosis of hepatic encephalopathy were selected for this trial. Patients having an allergy to rifaximin, recent alcohol use, prior antibiotic or psychoactive drug use, history of portosystemic shunt surgery, uncontrolled comorbidities, malignancies, pregnancy, or participation in other clinical trials within the preceding three months were not included to avoid potential bias. Patients underwent three assessments: an initial screening, a four-week follow-up, and an eight-week evaluation. The baseline visit involved a thorough medical history, physical examination, and laboratory assessments, including complete blood

count, liver and kidney function tests, prothrombin time index, blood glucose levels, electrolytes, and abdominal ultrasound. Hepatic encephalopathy was evaluated using the Mini-Mental State Examination (MMSE) psychometric hepatic encephalopathy score (PHES) and the Stroop test.

The same clinical and laboratory parameters were reassessed during follow-ups to track disease progression and treatment response. Data were collected systematically using predesigned questionnaires.

Statistical analysis was conducted using SPSS version 22 with descriptive statistics expressed as mean ± standard deviation for continuous variables and as frequencies and percentages for categorical variables. Chi-square test was applied to compare recurrence rates between the two groups with a significance threshold set at $P < 0.05$. Stratification was performed to control for effect modifiers such as age, gender, BMI, and education level, ensuring robust analytical outcomes.

RESULTS

Group A, receiving 550 mg of rifaximin daily, consisted of 80 participants with an average age of 46.60±16.967 years and an average body mass index of 23.7625±2.53204 kg/m². Group B, treated with 1100 mg of rifaximin daily, also included 80 participants with a mean age of 48.37±14.237 years and a mean body mass index of 24.4500±2.61398 kg/m².

Figure 1 depicts the age distribution of the patients in both groups.

Table 1 presents the demographic features of patients enrolled in both groups, including gender, marital status, and education level.

As for the recurrence of hepatic encephalopathy which was our key focus we found that in Group A (550 mg/day) 38 participants (47.5%) experienced a recurrence of either covert or overt hepatic encephalopathy while 42 (52.5%) did not, in Group B (1100 mg/day), 35 participants (43.8%) had a recurrence and 45 (56.2.5%) did not. Combining both groups, 73 participants (45.6%) across the 160 analyzed experienced a recurrence, while 87 (54.4%) remained free of recurrence, summing to 160 (100.0%). However the difference in recurrence rates between the two groups did not reach statistical significance ($P = 0.63$) (Table 2). We did not observe notable differences in terms of gender ($P > 0.05$), education level ($P > 0.05$), and BMI ($P > 0.05$), except for age ($P = 0.01$).

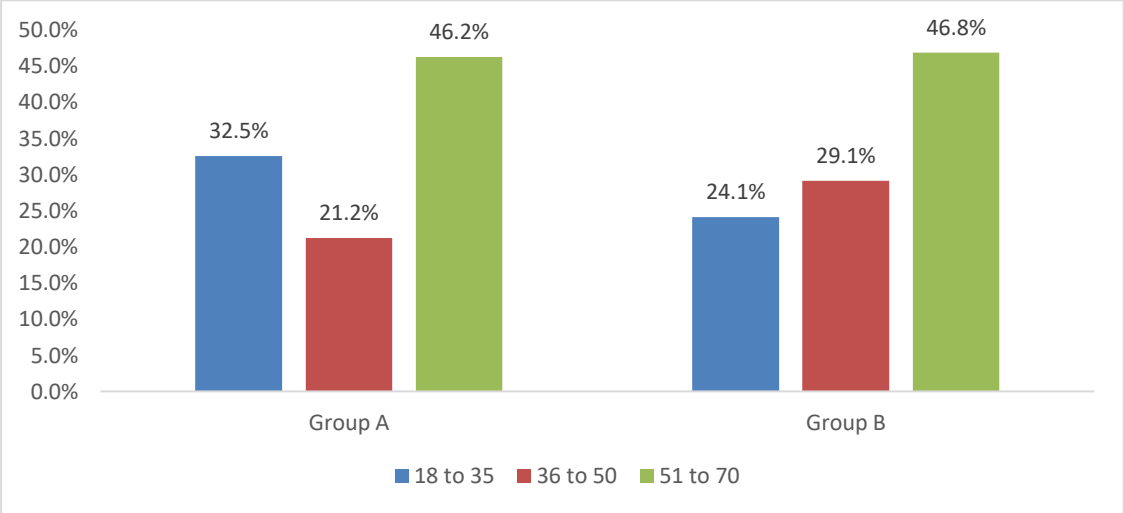

Figure 1: Distribution of age groups between both groups

Table 1: Demographics

Demographics		Groups			
		Group A (550 mg/Day)		Group B (1100 mg/Day)	
		N	%	N	%
Gender	Male	46	57.5%	44	55.0%
	Female	34	42.5%	36	45.0%
Education level	Primary	30	37.5%	24	30.0%
	Secondary	21	26.2%	31	38.8%
	High	29	36.2%	25	31.2%
Marital status	Married	57	71.2%	50	62.5%
	Unmarried	23	28.8%	30	37.5%

Table 2: Comparison of recurrence between both groups

		Recurrence of covert and overt HE		Total	P value
		Yes	No		
Groups	Group A (550 mg/Day)	38	42	80	0.63
		47.5%	52.5%	100.0%	
	Group B (1100 mg/Day)	35	45	80	
		43.8%	56.2%	100.0%	
Total		73	87	160	
		45.6%	54.4%	100.0%	

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Table 3: Association of recurrence of covert and overt HE w.r.t age

Age groups (Years)			Recurrence of covert and overt HE		Total	P value
			Yes	No		
18 to 35	Groups	Group A (550 mg/Day)	12	14	26	0.01
			46.2%	53.8%	100.0%	
		Group B (1100 mg/Day)	2	17	19	
			10.5%	89.5%	100.0%	
	Total		14	31	45	
			31.1%	68.9%	100.0%	
36 to 50	Groups	Group A (550 mg/Day)	9	8	17	P > 0.05
			52.9%	47.1%	100.0%	
		Group B (1100 mg/Day)	9	14	23	
			39.1%	60.9%	100.0%	
	Total		18	22	40	
			45.0%	55.0%	100.0%	
51 to 70	Groups	Group A (550 mg/Day)	17	20	37	P > 0.05
			45.9%	54.1%	100.0%	
		Group B (1100 mg/Day)	24	14	38	
			63.2%	36.8%	100.0%	
	Total		41	34	75	
			54.7%	45.3%	100.0%	

DISCUSSION

Based on the findings from our study and the supporting literature, it is evident that while rifaximin plays a crucial role in HE management, increasing the dosage does not necessarily translate into a significant reduction in recurrence rates or improved patient outcomes.

The demographic analysis of our study indicates that both treatment groups, which were Group A (550 mg/day) and Group B (1100 mg/day), exhibited similar baseline characteristics. The mean age and body mass index (BMI) were comparable, with Group A having an average age of 46.60±16.967 years and a BMI of 23.76±2.53 kg/m², while Group B had a mean age of 48.37±14.237 years and a BMI of 24.45±2.61 kg/m². The gender distribution was also similar between the groups ensuring that confounding variables related to age weight and gender were minimized.

Recurrence of HE was the primary outcome of our interest in this study. In Group A, 47.5% of patients experienced a slightly higher recurrence rate, while in Group B, the recurrence rate was comparatively low at 43.8%. Although a marginal increase was observed in the lower-dose group, this difference did not reach a level of statistical significance (P = 0.63), suggesting that increasing the dose to 1100 mg/day did not confer a substantial beneficial effect against recurrence.

These findings align with previous research. For instance, a study by Khokhar et al. compared once-daily 550 mg rifaximin to a twice-daily 550 mg regimen and found no marked difference in preventing HE recurrence (P = 0.088) (13). Similarly, Tan et al., evaluated low-dose (800 mg/day) versus high-dose (1200 mg/day) rifaximin for covert HE and concluded that both doses had comparable efficacy in improving neurocognitive function. [12] These studies reinforce the notion that while rifaximin is effective in HE prevention, escalating the dosage does not yield substantial additional benefits.

The lack of significant difference in recurrence rates between the two doses can be attributed to rifaximin's pharmacokinetics. As a non-absorbable antibiotic rifaximin exerts its effects within the gastrointestinal tract by altering the gut microbiota and reducing ammonia production. Once a threshold effect is reached increasing the dose further may not provide additional benefits. The findings of Perrone et al. also suggest that rifaximin 550 mg is associated with high treatment persistence and adherence reinforcing its role as the standard dosing regimen (14). Studies have also highlighted that the morality rates between both regimes did not differ at a notable level. A study by Sarwar et al., showed that mortality rates between the groups (17.6% in the 550 mg group vs. 17.07% in the 1100 mg group) were not statistically notable (15). This has also been confirmed by Habib et al. who found that mortality rates did not differ remarkably between high-dose and low-dose rifaximin groups suggesting that higher doses do not necessarily improve survival outcomes in these patients (16).

Considering these findings our recommendation would be to follow the standard 550 mg daily rifaximin regimen for HE prevention. Increasing the dose to 1100 mg/day does not appear to provide a clinical advantage but may contribute to increased treatment costs and potential medication burden. Future research should explore patient-specific factors that may influence rifaximin's efficacy such as gut microbiome composition and individualized ammonia metabolism rates.

Overall, our study corroborates existing evidence that supports the use of rifaximin at the standard 550 mg daily dose for HE prevention. While rifaximin remains a cornerstone in HE management its dose escalation beyond the recommended regimen does not significantly impact recurrence rates mortality or overall patient outcomes.

CONCLUSION

Our study found that hepatic encephalopathy recurrence occurred in 47.5% patients receiving 550 mg/day rifaximin and 43.8% patients on 1100 mg/day having no notable difference (P = 0.63). Given the comparable efficacy between both regimes, the standard 550 mg daily regimen remains the optimal choice for secondary prevention. Future research should focus on individualized treatment strategies rather than dose escalation.

DECLARATIONS

Data Availability Statement

All data generated or analysed during the study are included in the manuscript.

Ethics approval and consent to participate

Approved by the department Concerned. (IRBEC-SZMCHR-24)

Consent for publication

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CONFLICT OF INTEREST

The authors declared an absence of conflict of interest.

AUTHOR CONTRIBUTION

NAZIA BIBI (Postgraduate Resident)
Manuscript Drafting, Data entry, Data Analysis, Study Design, Manuscript revisions, and Review of Literature.
MOEEN AKHTAR MALIK (Associate Professor)
Conception of Study, Development of Research Methodology Design, Critical input, and Final approval of manuscript.
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