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Original Research Article

Comparison of the Efficacy of Rifaximin Versus Metronidazole in Patients With Hepatic Encephalopathy at a Tertiary Care Hospital

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Abstract: *Hepatic encephalopathy (HE) is a serious neurocognitive complication of liver cirrhosis, contributing substantially to morbidity, hospitalizations, and mortality. Antibiotics such as rifaximin and metronidazole are widely used to reduce gut-derived ammonia; however, evidence regarding their comparative efficacy in acute HE remains inconsistent, particularly in South Asian populations. This study evaluated and compared the effectiveness of rifaximin and metronidazole in patients with hepatic encephalopathy admitted to a tertiary care hospital in Pakistan.* ***Objective:*** *To compare the efficacy of rifaximin versus metronidazole in patients with hepatic encephalopathy using the West Haven criteria.* ***Methods:*** *A randomized controlled trial was conducted in the Department of Medicine, Sheikh Zayed Hospital, Rahim Yar Khan. Ninety patients aged 20–70 years presenting within 48 hours of the onset of hepatic encephalopathy were enrolled and randomly allocated into two groups: Group A received intravenous metronidazole 500 mg every eight hours, while Group B received rifaximin 550 mg twice daily. Both treatments were administered for seven days. Efficacy was defined as an improvement of at least one grade on the West Haven scale. Demographic variables, comorbidities, and baseline HE grades were recorded. Data were analyzed using SPSS version 25, with the Chi-square test used to compare efficacy between groups.* ***Results:*** *The cohort's mean age was 54.2 ± 9.8 years, with males accounting for 67.8%. Baseline characteristics, including comorbidities and HE grades, were comparable between groups. After 7 days of treatment, efficacy was significantly higher in the metronidazole group, with 75.6% of patients demonstrating improvement, compared with 42.2% in the rifaximin group (p = 0.002). Stratified analysis showed consistent superiority of metronidazole across gender, diabetes, hypertension, and HE Grades II and III. No significant adverse effects were reported in either treatment group.* ***Conclusion:*** *Metronidazole was significantly more effective than rifaximin in improving hepatic encephalopathy over a seven-day treatment period. These findings support the preferential use of metronidazole for acute HE management in resource-limited settings such as Pakistan, where cost-effective and rapidly acting treatment options are essential.*

Keywords: Pregabalin, Hemodynamics, Pneumoperitoneum

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Introduction

Hepatic encephalopathy (HE) is a complex neurocognitive disorder associated with liver failure, characterized by a spectrum of neurological dysfunction ranging from mild cognitive impairment to marked confusion and coma. Its prevalence significantly increases in patients with liver cirrhosis, affecting both quality of life and survival rates. Indeed, studies indicate that approximately 30-50% of patients with cirrhosis experience HE as a complication (1), and HE exacerbates hospitalizations and healthcare costs, underlining the need for effective treatments (2). The cornerstone of HE management involves therapeutic approaches such as non-absorbable disaccharides (e.g., lactulose) and antibiotics, particularly rifaximin, which has garnered attention for its efficacy and safety profile (3).

Rifaximin, an oral non-systemic antibiotic with broad-spectrum activity, is posited to modify gut microbiota and reduce the absorption of ammonia, a key contributor to HE (4). Unlike traditional antibiotics, rifaximin is minimally absorbed in the gastrointestinal tract and is excreted unchanged [5]. Its safety and efficacy have been validated in multiple studies, demonstrating a significant reduction in HE recurrence and related hospitalizations (6, 7). Conversely, metronidazole, another antibiotic with potential use in HE, is associated with specific adverse neurological effects, which may limit its long-term applicability in HE patients (8).

A comparative study has demonstrated that rifaximin, when combined with lactulose, significantly improves the resolution of overt hepatic encephalopathy compared with metronidazole, providing an adjunctive option for the long-term management of this condition (9, 10). Specifically, rifaximin has been shown to achieve resolution rates of 75% within a defined treatment period, compared with around 50% with traditional therapies such as metronidazole (9). Moreover, patients on rifaximin had lower hospitalization rates and better cognitive outcomes (11). These findings provide a robust argument for the preferential use of rifaximin over metronidazole in the management of HE.

Given the unique socio-economic challenges faced by the Pakistani population, such as limited access to healthcare resources and the burden of liver disease, evaluating these antibiotics' efficacy in a Pakistani context is pertinent. The prevalence of liver cirrhosis and its complications, including HE, continues to rise in Pakistan due to increasing rates of hepatitis C infection and alcohol-related liver disease. This underscores the critical need for effective, safe, and accessible treatment options for HE at tertiary care facilities nationwide.

Understanding the comparative efficacy of rifaximin versus metronidazole is pivotal for formulating evidence-based treatment protocols that consider the local epidemiology and resource availability. Thus, this study aims to evaluate the effectiveness of rifaximin versus metronidazole in treating patients with hepatic encephalopathy at a tertiary care hospital in Pakistan, thereby contributing to improved management strategies for this debilitating condition.

Methodology

The study was designed as a randomized controlled trial and conducted in the Department of Medicine at Sheikh Zayed Hospital, Rahim Yar

Khan, a major tertiary care institution serving both urban and rural populations of Southern Punjab. The trial was conducted over three months, from 13 February to 13 May 2025, following approval from the institutional ethical review committee and registration with the College of Physicians and Surgeons of Pakistan. Patients presenting with hepatic encephalopathy within forty-eight hours of symptom onset were screened through consecutive sampling. Eligibility was based on a clinical diagnosis of hepatic encephalopathy secondary to liver cirrhosis, with grading performed according to the West Haven criteria. Individuals aged 20 to 70 years, regardless of gender, were considered for inclusion. Patients with known intracranial pathology such as meningitis, encephalitis, or stroke, those with chronic kidney disease, recent exposure to either study drug within the preceding month, ongoing use of neuropsychiatric medications, or documented drug allergies were excluded. Written informed consent was obtained from all eligible participants after explaining the purpose, procedures, and potential benefits of the study.

After enrollment, baseline demographic and clinical data—including age, gender, BMI, residential status (urban or rural), presence of diabetes mellitus, hypertension, obesity, and initial HE grade—were recorded using a structured proforma. Participants were randomly assigned via lottery to one of two treatment arms. Patients assigned to Group A received intravenous metronidazole at a dose of 500 milligrams every 8 hours. In comparison, those assigned to Group B received rifaximin 550 milligrams twice daily via nasogastric tube. Both interventions were continued for seven days, and all patients received standard supportive care for hepatic encephalopathy, including correction of precipitating factors as per hospital protocol. Clinical assessment of hepatic encephalopathy was repeated on the seventh day of therapy by an attending physician blinded to treatment allocation. The primary outcome was efficacy, defined as improvement of at least 1 grade on the West Haven scale from baseline to day 7.

All collected data were entered and analyzed using SPSS version 25. Continuous variables such as age and BMI were analyzed as mean and standard deviation. In contrast, categorical variables—including gender, comorbid conditions, residential status, obesity, baseline HE grade, and treatment efficacy—were summarized using frequencies and percentages. Comparison of treatment efficacy between the metronidazole and rifaximin groups was conducted using the chi-square test, with p-values < 0.05 considered statistically significant. Effect modifiers such as age, gender, diabetes, hypertension, obesity, residential status, and baseline HE grade were controlled for through stratified analysis, followed by post-stratification chi-square testing to assess the stability of the treatment effect across subgroups.

Results

The overall mean age of the cohort was 54.2 ± 9.8 years, and the majority of patients were between 51 and 60 years of age, representing the typical clinical spectrum of cirrhosis encountered in Pakistani tertiary-care hospitals. Male patients accounted for 67.8 %, reflecting the well-documented male predominance of chronic liver disease in the local population. Baseline demographic and clinical characteristics were comparable between the two groups, including gender distribution, comorbidities, and initial hepatic encephalopathy grades. Comorbidities were common; 38.9 % of patients had diabetes mellitus, 42.2 % had hypertension, and 21.1 % were obese. Exactly half of the patients were from rural areas, consistent with the catchment population of Sheikh Zayed Hospital, Rahim Yar Khan. At presentation, HE Grade II (42.2 %) and Grade III (34.4 %) were the most frequent baseline grades, and their distribution was similar in both treatment groups (Table 1).

A significant difference in treatment response was observed between the two groups. After 7 days of therapy, 75.6% of patients in the Metronidazole group showed at least a 1-grade improvement on the West Haven scale, compared with only 42.2% in the Rifaximin group ($p = 0.002$). This demonstrated a clear superiority of Metronidazole in achieving clinical improvement in hepatic encephalopathy (Table 2).

Stratified analysis further supported these findings. Among male patients, Metronidazole showed greater efficacy than Rifaximin, with 24 vs 13 improved cases, respectively, while similar trends were observed among female patients (10 vs 6 improved cases) (Table 3). When stratified by baseline HE grade, Metronidazole remained significantly more effective in Grades II and III, which represented the majority of the study population. Improvement was noted in 17 patients with Grade II and 11 patients with Grade III receiving Metronidazole, compared with substantially fewer responses in the Rifaximin group (Table 4).

Subgroup analyses based on comorbidities revealed consistent results. Patients with diabetes and hypertension demonstrated significantly higher improvement rates with Metronidazole compared to Rifaximin. Although the efficacy difference among obese patients did not reach statistical significance, the trend still favored Metronidazole (Table 5). No adverse drug reactions were observed in either group during the study period.

Table 1. Demographic and Baseline Characteristics of Study Participants (N = 90)

Variable	Metronidazole (n=45)	Rifaximin (n=45)	Total (N=90)
Age (years)	54.7 ± 10.1	53.8 ± 9.6	54.2 ± 9.8
Age Groups			
20–40 years	6 (13.3)	7 (15.6)	13 (14.4)
41–50 years	10 (22.2)	9 (20.0)	19 (21.1)
51–60 years	20 (44.4)	19 (42.2)	39 (43.3)
61–70 years	9 (20.0)	10 (22.2)	19 (21.1)
Gender			
Male	31 (68.9)	30 (66.7)	61 (67.8)
Female	14 (31.1)	15 (33.3)	29 (32.2)
Residential Status			
Rural	23 (51.1)	22 (48.9)	45 (50.0)
Urban	22 (48.9)	23 (51.1)	45 (50.0)
Comorbidities			
Diabetes Mellitus	17 (37.8)	18 (40.0)	35 (38.9)
Hypertension	20 (44.4)	18 (40.0)	38 (42.2)
Obesity	10 (22.2)	9 (20.0)	19 (21.1)
Baseline HE Grade			
Grade I	4 (8.9)	5 (11.1)	9 (10.0)
Grade II	19 (42.2)	19 (42.2)	38 (42.2)
Grade III	15 (33.3)	16 (35.6)	31 (34.4)

Grade IV	7 (15.6)	5 (11.1)	12 (13.3)

Table 2. Comparison of Treatment Efficacy between Groups (N = 90)

Treatment Group	Efficacy Yes n(%)	Efficacy No n(%)	p-value
Metronidazole (n=45)	34 (75.6)	11 (24.4)	0.002
Rifaximin (n=45)	19 (42.2)	26 (57.8)	

Table 3. Efficacy Stratified by Gender

Gender	Metronidazole Yes/No	Rifaximin Yes/No	p-value
Male (n=61)	24/7	13/17	0.01
Female (n=29)	10/4	6/9	0.04

Table 4. Efficacy Stratified by Baseline HE Grade

HE Grade	Metronidazole Yes/No	Rifaximin Yes/No	p-value
Grade I	4/0	3/2	0.28
Grade II	17/2	10/9	0.01
Grade III	11/4	5/11	0.03
Grade IV	2/5	1/4	0.67

Table 5. Efficacy Stratified by Comorbidities

Comorbidity	Metronidazole Yes/No	Rifaximin Yes/No	p-value
Diabetes (n=35)	12/5	6/12	0.02
Hypertension (n=38)	14/6	7/11	0.04
Obesity (n=19)	6/4	3/6	0.22

Discussion

The results of the current study provide critical insights into the comparative efficacy of metronidazole and rifaximin in treating hepatic encephalopathy (HE) among patients with liver cirrhosis at a tertiary care facility in Pakistan. The demographic characteristics of the patient cohort align with the global literature, with a mean age of 54.2 ± 9.8 years and a male predominance of 67.8%. This is somewhat consistent with the findings of Tapper et al. 12, who reported similar gender distributions among cirrhotic patients. The prevalence of commonly associated comorbidities such as diabetes mellitus (38.9%), hypertension (42.2%), and obesity (21.1%) further correlates with prior studies emphasizing the multifactorial risks contributing to HE in patients with liver disease, consistent with findings by Yoshiji et al. (13).

In our study, after 7 days of treatment, the metronidazole group showed a 75.6% improvement rate. In contrast, the rifaximin group showed only 42.2% improvement ($p = 0.002$), indicating a notable difference in efficacy. This finding is consistent with the evidence presented by Iwasa et al. (14), who reported metronidazole's comparative effectiveness. Additionally, our results reflect a trend noted by Patel et al. (15), in which metronidazole showed superior clinical improvement in patients with Grade II and III HE, corroborating our stratified analysis, which identified better outcomes among these patient grades ($p = 0.01$ for Grade II and $p = 0.03$ for Grade III).

Interestingly, stratified analyses indicated that metronidazole's superior efficacy was consistent across gender and comorbidities. Male participants had 24 cases improve with metronidazole compared with 13 with rifaximin, consistent with the findings of Seifert et al. Seifert et al. (16) highlighted the merits of metronidazole in male-dominated cohorts. In patients with diabetes and hypertension, our results showed significantly higher improvement rates with metronidazole ($p = 0.02$ for diabetes and $p = 0.04$ for hypertension), reflecting its effectiveness in managing HE, likely due to its rapid effect on gut-derived toxins (17).

Conversely, despite rifaximin's established role as a non-systemic antibiotic for managing HE, our study highlights its limitations in achieving significant clinical improvement compared with metronidazole during the acute phase of HE treatment. The findings align with the literature, indicating that while rifaximin reduces the recurrence of HE in long-term settings 18, its immediate efficacy appears less pronounced, particularly in non-combined therapy contexts where adjunctive treatment strategies such as lactulose are absent (19). Previous research supports this notion, emphasizing that rifaximin is more successful in a preventive role rather than as a treatment modality (20).

Moreover, the absence of adverse drug reactions in both treatment groups signifies a favorable safety profile for both metronidazole and rifaximin, further highlighting the importance of personalized treatment approaches. This complements findings from established studies demonstrating that the incidence of adverse events associated with both medications is minimal, although neurotoxicity inherent to metronidazole usage remains a clinical concern (21).

Given the increasing prevalence of liver diseases and their complications in Pakistan, particularly in rural areas where healthcare access is limited, understanding the treatment efficacy differences becomes crucial. The demographic similarities between our study and the existing literature underscore the need for tailored pharmacotherapy strategies in the Pakistani context. Furthermore, this research contributes to the ongoing discourse on the clinical management of HE and emphasizes the pressing need for systematic implementation of effective treatment protocols in Pakistan's healthcare facilities (22).

As a significant focus lies on improving outcomes in patients with liver complications, particularly HE, our findings suggest the potential to continue metronidazole for acute cases while integrating rifaximin into longer-term management plans for prevention. Holistic treatment protocols that incorporate local epidemiological data, including prevalent comorbidities and patient demographics, can enhance the clinical approach to managing HE in the community.

This study reinforces metronidazole's efficacy as a superior treatment option compared to rifaximin for the acute management of hepatic encephalopathy in a Pakistani cohort. As practitioners navigate the complexities of liver disease management amid rising incidence rates, adopting evidence-based treatment modalities is essential to improving patient outcomes.

Conclusion

This randomized controlled trial demonstrates that metronidazole is significantly more effective than rifaximin for short-term improvement in hepatic encephalopathy, with 75.6% of patients achieving clinical recovery compared with 42.2% in the rifaximin group. The superiority of metronidazole was consistent across major demographic and clinical

subgroups, including patients with HE Grades II and III. In the context of Pakistan's healthcare landscape—where affordability, rapid symptom resolution, and accessibility are critical—metronidazole offers a practical and clinically advantageous option for acute HE management. These findings highlight the importance of integrating metronidazole into standard treatment protocols for hepatic encephalopathy in tertiary care settings and call for further multicenter studies to validate these results across broader populations.

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-SZHRYKH-0218-24)
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Not applicable

Conflict of interest

The authors declared no conflicts of interest.

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All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the integrity of the study.

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