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COMPARISON OF EFFICACY OF METRONIDAZOLE VERSUS RIFAXIMIN IN TREATMENT OF HEPATIC ENCEPHALOPATHY

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ABSTRACT

Background: Hepatic encephalopathy (HE) is a severe neuropsychiatric disorder of liver cirrhosis, which is manifested by alterations in state of mind and neurological deficits caused by the accumulation of neurotoxins, including ammonia. Some of the treatment methods applied in the management of this condition include Rifaximin, which is a non-absorbable antibiotic, and metronidazole, which is a systemic antimicrobial agent.

Objective: To compare the effectiveness of rifaximin and metronidazole in treating the hepatic encephalopathy in pediatric patients.

Methods: This randomized controlled trial was done in the Department of Pediatrics of Children's Hospital and Institute of Child Health, Faisalabad from June 2025 to September 2025. Two hundred four children aged 1-14 years with hepatic encephalopathy were recruited through non-probability consecutive sampling and were randomly given two equal groups. Group A was treated with rifaximin (220mg) twice a day through nasogastric tube and Group B was treated using intravenous metronidazole (1.5mg/kg) every 8 hours during five days. Day 5 in the West Haven criteria was selected to determine the efficacy of the treatment based on the improvement in the grade of the HE. Data analysis was done through SPSS 25. The efficacy of the two groups was compared through the chi-square test, and p not less than 0.05 was assumed to be statistically significant.

Results: Out of the 204 respondents, 118 (57.8%) individuals were male and 86 (42.2%) female. The age mean of the rifaximin group was 7.9 years and the age of the metronidazole group was 8.2 years ($p = 0.62$). The high-effect of the treatment was seen in 95 (93.1%) and 82 (80.4%) of the patients who had been given rifaximin and metronidazole respectively. The difference was found to be significant ($\chi^2 = 7.11$, $p = 0.008$) which mean that the efficacy of rifaximin is superior. The efficacy of rifaximin was found to be higher in both age groups, and the statistically significant results were found in 8-14-year age ($p = 0.04$) group whereas gender and BMI did not seem to significantly raise or lower the treatment outcomes.

Conclusion: Rifaximin showed high efficacy when used in the treatment of pediatric hepatic encephalopathy, in comparison to metronidazole. Rifaximin can be used for treatment of hepatic encephalopathy in pediatric patients because of its excellent treatment response and good safety profile.

INTRODUCTION

Hepatic encephalopathy (HE) is a well-known clinical disorder of liver cirrhosis and early detection of gel-cutting attending factors are very significant in the diagnosis and therapy of this deadly disorder (Ohikere & Wong, 2024). HE grows in 50% of the patients with cirrhosis and its presence is a poor prognostic figurel. There are primarily precipitating factors, which are represented by infections, gastrointestinal bleeding, constipation, electrolyte disorders, renal dysfunction, and hepatotoxic agents (Li et al., 2018). The underlying pathophysiologic basics include that as a result of the elevated production of ammonia. The first symptom of hepatic encephalopathy is altered sleep. The other

clinical signs are flapping tremor, hyperreflexia, irritability, drowsiness and decerebrate posture with or without altered mental status and irrelevant talks (Wang et al., 2013). There are several therapeutic alternatives that have been attempted previously with different levels of success rate and adverse effects. The modalities used include Neomycin, Enema, Lactulose, Metronidazole, Vancomycin, Rifaxamin etc. Both metronidazole and rifaximin are antibiotics and also possess potentral activlity against the bacteria present in the gut which are responsible for production of ammonia and other neurotoxic substances in the intestines (Bajaj et al., 2018). Rifaximin is a nonabsorbable antibiotic that has good safety profile (Scarpignato & Pelosini, 2005). A comparative study of effectiveness of metronidazole and rifaximin on patients with hepatic encephalopathy showed that the efficacy of metronidazole was 80% and rifaximin was 93.37% (Mekky et al., 2018). The objective of the study is to establish the relative efficacy of metronidazole and rifaximin among patients with hepatic encephalopathy. The comparative study based on role of metronidaz ole and rifaximin would be valuable evidence that would inform clinicians to make evidence-based treatment choices. The results of the study can be used to suggest the most appropriate antibiotic treatment of patients with hepatic encephalopathy. This is aimed to compare the efficacy of Metronidazole and Rifaxamine in the treatment of hepatic encephalopathy.

METHOD

Study Design and Setting
The study was a randomized controlled trial which was conducted at the Department of Pediatrics, Children's Hospital and Institute of Child Health, Faisalabad from June 2025 to September 2025

Sample Size Calculation
The sample size was determined by using the sample size calculator in the World Health Organization (WHO) to comparatively determine two proportions. Based on a significant level (α) of 5%, power of 80%, expected efficacy of metronidazole of 80%, and expected efficacy of rifaximin of 93.3%, a sample size of 204 patients was determined and 102 of patients assigned to each group.

Sampling Technique
Non probability consecutive sampling method was used to recruit the eligible participants.

Inclusion Criteria
- Children of either gender
- Age between 1 and 14 years
- Hepatic encephalopathy identified given operational predefined criteria.

Exclusion Criteria
- Known hypersensitivity or allergy metronidazole or rifaximin.
- Existence of major central nervous system diseases (e.g. meningitis, encephalitis)
- Cerebral vascular accident history.
- Clinical history and complete blood count findings evidence of septicemia.

Ethical Considerations
Before starting study, the Ethical approval was gained. Parental or legal guardian informed consent was taken before enrollment. The privacy of patient data was highly administered in the study.

Randomization and Intervention.
To attain equal distribution of eligible participants, there was a lottery approach of assigning the individuals to Group A and Group B. Group A (Rifaximinet system): The patients were in rifaximin group where they were administered with rifaximin 220mg two times a day with nasogastric tube over a period of five days. Group B (Metronidazole group): The group received intravenous metronidazole at 1.5mg/kg dose per dose with every 8 hours during five days. The detection and classification of hepatic encephalopathy was determined based on a detailed clinical history, physical examination, and observation based on West Haven criteria.

Outcome Measurement
Efficacy of treatment on day 5 was the major result, which was measured based on the operational definition named. The response of treatment was recorded as effective or not. All the clinical and demographic information was noted onto a structured proforma.

Statistical Analysis

The SPSS version 25.0 was used to analyze the data. The age, weight and the period of liver cirrhosis are quantitative variables that were stated in terms of the mean and standard deviation. Categorical variables such as the sex, level of encephalopathy and efficacy of the treatment were shown in form of frequencies and percentages. Chi-square test was used to compare the efficacy of the treatment on the two groups. Stratification was used to balance effects modifiers such as age, gender, and body mass index (BMI). Chi-square testing that was done after stratification was done to determine their presuppositions on the treatment outcomes. The p-value of 0.05 or less had been regarded as significant .

RESULTS

This study registered 204 pediatric patients with hepatic encephalopathy (HE). It was used randomly to separate patients into two groups (Group A Rifaximin (n = 102) and Group B Metronidazole (n =102). Every patient underwent the 5 days course of treatment and none of the patients dropped out.

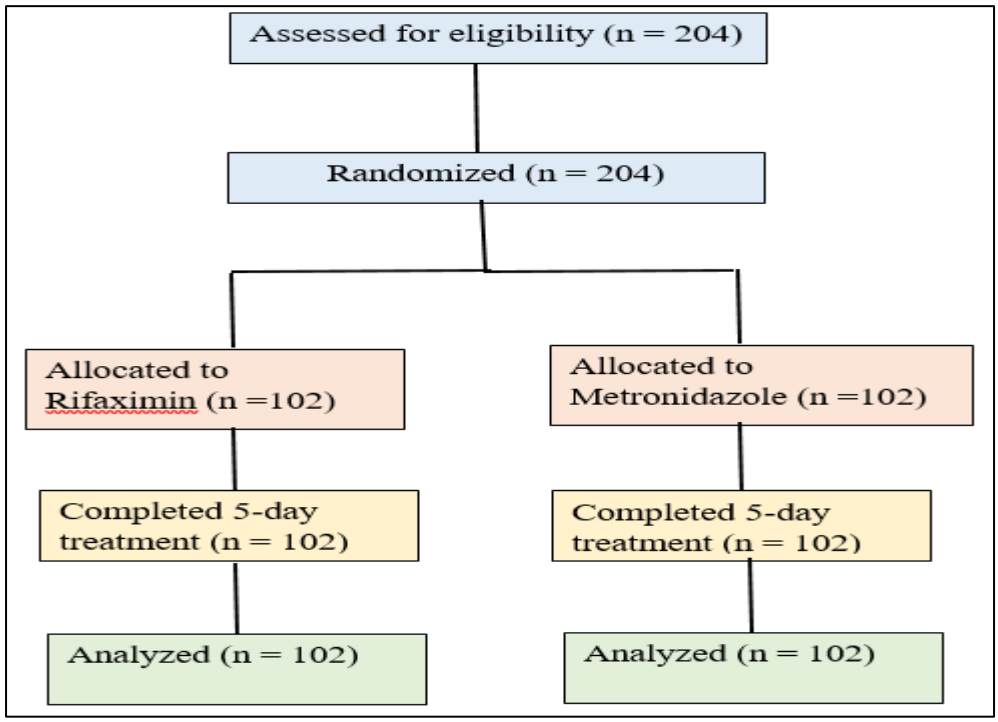

Figure1: Flow diagram of patient study during research.

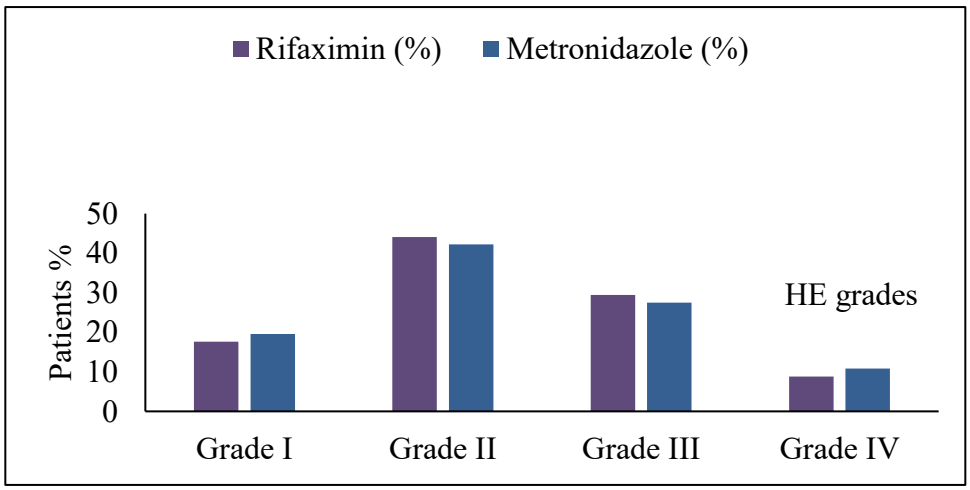

Figure 2: HE Grade I-IV: These grade denoted the severity per West Haven criteria. The baseline had most patients in both groups of moderate to severe HE.

Baseline Characteristics

Table 1 provides the baseline demographic and clinical data of patients. The average age of the patients in the Rifaximin group was 7.9 ±3.4 years, whereas in Metronidazole group the mean age was 8.2 ±3.6 years. The age difference between the groups was not statistically significant (p = 0.62). Among 204 patients, 118 (57.8%) were male and 86 (42.2%) were female, and no significant difference in the gender of patients in the two groups (p = 0.77). There was no significant difference in the mean body mass index (BMI) between the patients receiving Rifaximin and the patients receiving Metronidazole (17.8± 2.3 kg/m 2 vs 18.1± 2.5 kg/m 2, respectively, p = 0.48).

Table 1: Basic demographics of the studied participant (n = 204)

Variable	Group A (Rifaximin) n (%)	Group B (Metronidazole) n (%)	P-value
Age (years), Mean ± SD	7.9 ± 3.4	8.2 ± 3.6	0.62
Male	60 (58.8%)	58 (56.9%)	0.77
Female	42 (41.2%)	44 (43.1%)	–
BMI (kg/m²), Mean ± SD	17.8 ± 2.3	18.1 ± 2.5	0.48

Treatment Efficacy

It was measured on Day 5 based on the operational definition (clinical improvement in HE grade). Rifaximin group: 95/102 (93.1%) patients improved clinically. Metronidazole group: 82/102 patients (80.4%) improved. Chi-square test showed that the two groups had significant difference which was statistically significant because of Chi square = 7.11, p = 0.008, which shows that Rifaximin was more effective in the treatment of pediatric HE, compared to Metronidazole.

Table 2: Comparison of Efficacy of treatment groups.

Outcome	Group A (Rifaximin) n (%)	Group B (Metronidazole) n (%)	P-value
Effective	95 (93.1%)	82 (80.4%)	0.008
Not Effective	7 (6.9%)	20 (19.6%)	–

Stratification Analysis

Stratification was done to ensure the control of the possible modifiers of effect; age, gender and BMI. The efficacy was considered under two age groups, 1-7 years and 8-14 years. The efficacy of Rifaximin was higher in the two age groups. There was statistically significant superiority in the older age group (8-14 years old) (p = 0.04).

Table 3: Stratified Effective Analysis with Age Group.

Age Group	Rifaximin Effective n (%)	Metronidazole Effective n (%)	P-value
1–7 years	48 (92.3%)	41 (78.8%)	0.06
8–14 years	47 (94.0%)	41 (82.0%)	0.04

DISCUSSION

Hepatic encephalopathy (HE) is a life threatening and severe complication of liver disease among children (Ravindranath et al., 2024). The current randomized balanced trial evaluated the efficacy of rifaximin and metronidazole in the treatment of pediatric HE and established proved that rifaximin was more effective than metronidazole.

In the present research, the clinical improvement rate recorded was of rifaximine 93.1% versus 80.4% in the metronidazole group (p = 0.008). This is in agreement with previous research studies which suggested increased efficacy of rifaximine in terms of severity and recurrence of HE. The increased response rate with rifaximin could be explained by intraluminal specific activity of the substance, weak systemic penetration, and positive safety index (Tsakiridou et al., 2025). Rifaximin treats the underlying pathophysiological mechanism of HE, by decreasing intestinal ammonia-forming bacteria with minimal adverse effects on the body system (Chen et al., 2021) .

Even though Metronidazole as the agent proved to be effective in the reduction of the anaerobic bacterial load, its efficacy was relatively lower. Its systematic uptake and the possibility of reduction neurotoxicity with extended use may restrain its treatment benefit (Löfmark et al., 2010). Although short-term administration in our case was typically well tolerated, it is both theoretically and practically safe, which is benefited by non-absorbable rifaximin especially in children (Chang, 2018).

Notably, the demographic and clinical details of the baseline such as age, gender ratio, body mass index, and HE grade were similar in the two groups. The majority of the patients were Grade II or III HE, which showed moderate to severe disease at the time of admission. The similarity in the baseline distribution is in the support of internal validity of our results.

Rifaximin was more effective in both age groups (17 years and 8 years). Statistical significance was identified in older age group ($p = 0.04$), whereas there was strong tendency of statistical significance in younger age group ($p = 0.06$). This can imply a greater therapeutic responsiveness of older children, perhaps because of the variability of severity of the disease, or drug metabolism or adherence to supporting care interventions (Marsot, 2018). Nevertheless, gender and BMI did not have a significant effect on modulation of treatment response, and, therefore, the effect of the superiority of rifaximin was similar within these subgroups.

The results of this analysis match the already existing comparative studies in terms of efficiency of around 93 percent of rifaximin and 80 percent of metronidazole. The statistically significant difference noted is a reinforcement of the increasing literature supporting the use of rifaximin as a first-line agent against microorganisms during the management of HE.

Regardless of these strengths, there are some limitations that are to be mentioned. First, the research was carried out in one center, and this could restrict the extent of generalization. Second, follow-up was carried out within five days; thus, no long-term results, recurrence, and safety were assessed. Third, the quantitative measure of ammonia as a biochemical outcome parameter was not determined and the primary outcome used was clinical improvement. Prospective multicenter studies with a longer follow-up time, and the use of a biochemical marker would present a more detailed evidence.

CONCLUSION

Conclusively, rifaximin was shown to have a much greater efficacy than metronidazole in the treatment of pediatric hepatic encephalopathy. Since rifampicin has a higher response rate and better safety profile, it can be regarded as one of the treatment choices in this group of patients. These results and the analysis of long-term results should be pivoted by further massive studies.

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