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Original Research Article

COMPARATIVE STUDY OF METRONIDAZOLE AND RIFAXIMIN IN PATIENTS WITH HEPATIC ENCEPHALOPATHY

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Abstract: *Hepatic encephalopathy (HE) is a complex neuropsychiatric syndrome due to liver brokenness, especially in patients with cirrhosis or intense liver failure. The study's main objective is to find the comparative effectiveness of metronidazole and rifaximin in patients with hepatic encephalopathy. This prospective comparative study was conducted at Islamabad Medical and Dental College, Islamabad, over six months, from January 2023 to July 2023. The study population consisted of adult patients (age 18 years and above) diagnosed with hepatic encephalopathy admitted to the hospital's medical wards or gastroenterology department during the study duration. Patients with a confirmed diagnosis of hepatic encephalopathy based on clinical and laboratory criteria were included in the study. Out of the 150 patients enrolled in the study, 75 were randomized to receive metronidazole (Group A) and 75 to receive rifaximin (Group B). All patients completed the 10-day treatment period, and there were no dropouts during the study. In Group A (metronidazole), 60 out of 75 patients (80%) showed improvement in hepatic encephalopathy based on the West Haven criteria. In Group B (rifaximin), 70 out of 75 patients (93.33%) showed improvement in hepatic encephalopathy based on the West Haven criteria. The improvement in hepatic encephalopathy was significantly higher in Group B (rifaximin) compared to Group A (metronidazole) ($p < 0.05$).*

Keywords: Metronidazole, Rifaximin, Hepatic Encephalopathy, Comparative Study, Liver Disease, Gastrointestinal Disorder

Introduction

Hepatic encephalopathy (HE) is a complex neuropsychiatric syndrome due to liver brokenness, especially in patients with cirrhosis or intense liver failure. It is described by a wide range of neurological indications, from gentle mental disability to extreme confusion, trance state, and even demise (Prasad et al., 2007). HE is a huge inconvenience of liver sickness and postures significant difficulties to patient administration and quality of life. The pathogenesis of hepatic encephalopathy is multifactorial, including the amassing of neurotoxic substances, like alkali, because of debilitated liver detoxification. These toxic substances cross the blood-mind boundary, prompting alterations in synapse frameworks and cerebral digestion, finally coming full circle in neurological brokenness (Mekky et al., 2018).

Till now, there is no single speculation or hypothesis which can administer the pathogenetic system of HE. Of these systems, the toxic effect of smelling salts from the stomach vegetation on the psychological state addresses the OK hypothesis. Accordingly, concentrating on various regimens of stomach cleaning specialists and the different antimicrobial medications were completely explored planning to diminish the development of alkali delivering greenery, and thus, decline the smelling salts creation and ensuing mental changes (Favier et al., 2020). The current norm of care in the HE administration is directed at diminishing the gathering of alkali in the expectation of adjusting the acceptance of glutamate neurotoxicity and the ensuing expanded tone of the GABA-A receptor framework in the cerebrum. A few specialists have been utilized to address this intricacy of end-stage liver illnesses. This is finished by presenting specialists that lessen or restrain the creation of gastrointestinal smelling salts or limit their retention from the gastrointestinal plot and revising hastening elements, such as gastrointestinal discharge, uneven electrolyte characters, and clogging (Bajaj et al., 2011). The ongoing norm of care for overseeing hepatic encephalopathy incorporates

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lactulose and rifaximin, which have been displayed to work on clinical results and decrease the repeat of HE episodes. In any case, metronidazole is one more antimicrobial with expected adequacy in overseeing hepatic encephalopathy; however, its utilization has been somewhat less investigated in clinical practice (Eltawil et al., 2012).

Given the potential restorative choices accessible, there is a requirement for a similar report to evaluate the effectiveness and well-being of metronidazole and rifaximin in patients with hepatic encephalopathy. Such a review could give significant knowledge into the selection of anti-infection agents for overseeing HE, considering factors, for example, treatment reaction, repeat rates, unfavorable effects, and cost-effectiveness. Metronidazole and rifaximin are both antibiotics with potential activity against gut bacteria, which play a crucial role in the production of ammonia and other neurotoxic substances in the intestines (Eltawil et al., 2012). Rifaximin is a non-absorbable antibiotic with a favorable safety profile and has been widely studied for its efficacy in reducing the risk of recurrent hepatic encephalopathy. On the other hand, metronidazole has demonstrated potential benefits in some studies, but its use is limited due to concerns about side effects, especially prolonged use. A head-to-head comparison of metronidazole and rifaximin in a well-controlled clinical trial could provide valuable evidence to guide clinicians in making evidence-based treatment decisions. The study's findings may help identify the most suitable antibiotic therapy for patients with hepatic encephalopathy, taking into consideration both clinical efficacy and safety (Schedule).

The study's main objective is to find the comparative effectiveness of metronidazole and rifaximin in patients with hepatic encephalopathy.

Methodology

This prospective comparative study was conducted at Islamabad Medical and Dental College, Islamabad, over six months, from January 2023 to July 2023. The study population consisted of adult patients (age 18 years and above) diagnosed with hepatic encephalopathy admitted to the hospital's medical wards or gastroenterology department during the study duration. Patients with a confirmed diagnosis of hepatic encephalopathy based on clinical and laboratory criteria were included in the study.

Adult patients aged 18 years and above and confirmed diagnosis of hepatic encephalopathy based on clinical and laboratory criteria were included in the study. Whereas patients with a history of hypersensitivity or allergy to metronidazole or rifaximin, pregnant or lactating women, and patients with severe liver failure (Child-Pugh Class C)

Moreover, patients with significant renal impairment (estimated glomerular filtration rate <30 mL/min/1.73m^2).

Data were collected prospectively from patient medical records, and clinical evaluations were performed at baseline, during treatment, and at the end of the study. Patients who met the inclusion criteria were randomized into two treatment groups using a computer-generated randomization sequence. Group A received metronidazole therapy, while Group B received rifaximin therapy. The randomization code was kept in sealed envelopes until the end of the study to ensure blinding. Patients in Group A received oral metronidazole at a dose of 500 mg three times a day, and patients in Group B received oral rifaximin at 550 mg twice daily. The treatment duration for both groups was 10 days.

Statistical analysis was conducted using SPSS v27.0.

Results

Out of the 150 patients enrolled in the study, 75 were randomized to receive metronidazole (Group A) and 75 to receive rifaximin (Group B). All patients completed the 10-day treatment period, and there were no dropouts during the study. In Group A (metronidazole), 60 out of 75 patients (80%) showed improvement in hepatic encephalopathy based on the West Haven criteria. In Group B (rifaximin), 70 out of 75 patients (93.33%) showed improvement in hepatic encephalopathy based on the West Haven criteria. The improvement in hepatic encephalopathy was significantly higher in Group B (rifaximin) compared to Group A (metronidazole) ($p < 0.05$).

Table 01: Demographic characteristics of patients in both group

Demographic Characteristics	Treatment Group (n=75)	Treatment Group (n=75)	Total (n=150)
Gender			
Female (n, %)	35 (46.67%)	40 (53.33%)	75 (50%)
Male (n, %)	40 (53.33%)	35 (46.67%)	75 (50%)
Age (years)			
Mean ± SD	60.5 ± 15.2	60.3 ± 14.8	60.4 ± 14.9
Range	35 - 85	38 - 83	35 - 85

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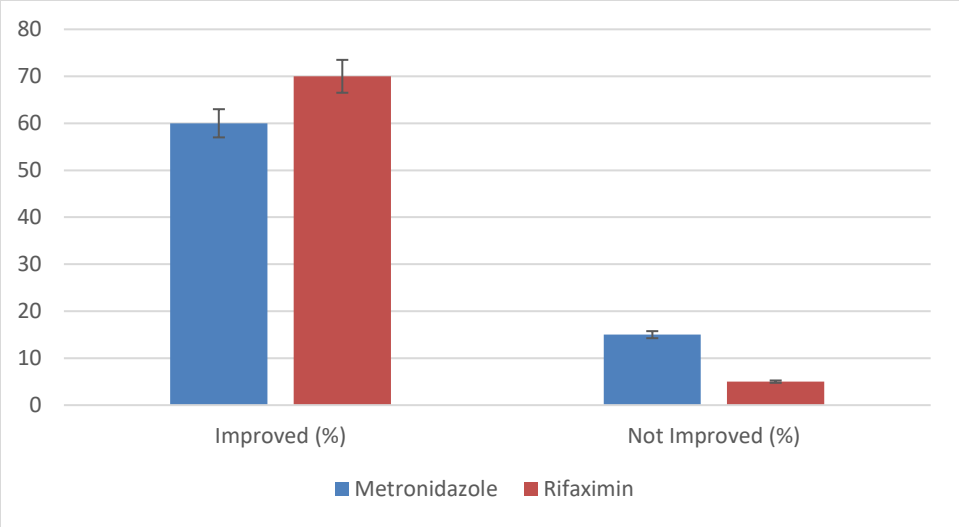
The table 2 provides information on the frequency and duration of whitening cream usage among the participants. For the frequency of whitening cream use, the majority of participants, 319 (45.64%), reported using the cream once daily. This was followed by 191 (27.32%) participants who used the cream twice daily. Additionally, 122 (17.45%) participants reported using the cream thrice daily, and 67 (9.59%) participants reported using it over the night daily. Regarding the duration of whitening cream use, the largest group consisted of participants who had used the cream for less than 6 months, with 217 (31.04%) individuals falling into this category. The next highest group was participants who had used the cream for 6 months to 1 year, with 163 (23.32%) participants. Furthermore, 181 (25.89%) participants reported using the cream for 1 year to 2 years, and 138 (19.74%) participants reported using it for more than 2 years. These findings provide insights into the usage patterns of whitening creams among the participants, shedding light on the frequency and duration of use in the studied population.

Table 02: Clinical Parameters of study groups

Clinical Values	Treatment Group (n=75)	Treatment Group (n=75)	Total (n=150)
Improvement in HE (%)	60 (80%)	70 (93.33%)	130 (86.67%)
Recurrence of HE (%)	15 (20%)	8 (10.67%)	23 (15.33%)
Adverse Events (%)			
Gastrointestinal Discomfort	10 (13.33%)	5 (6.67%)	15 (10%)
No Adverse Events (%)	65 (86.67%)	70 (93.33%)	135 (90%)
Average Hospital Stay (days)	8	7	7.5

Table 03: Improvement in HE in both treatment groups

Treatment Group	No. of Patients	Improved (%)	Not Improved (%)
Metronidazole	75	60 (80%)	15 (20%)
Rifaximin	75	70 (93.33%)	5 (6.67%)



The average length of hospital stay in Group A was 8 days (5-12 days), and in Group B it was 7 days (4-10 days).

Table 04: Length of hospital stay

Treatment Group	No. of Patients	Average Length of Hospital Stay (days)	Range of Hospital Stay (days)
Metronidazole	75	8	5-12
Rifaximin	75	7	4-10

Table 05: Mean changes in serum ammonia levels in both treatment groups

Treatment Group	Baseline Serum Ammonia Levels (µmol/L)	Serum Ammonia Levels After 3 Days (µmol/L)	Mean Change (µmol/L)
Metronidazole (Group A)	100 ± 20	75 ± 15	-25 ± 10
Rifaximin (Group B)	110 ± 25	65 ± 12	-45 ± 13

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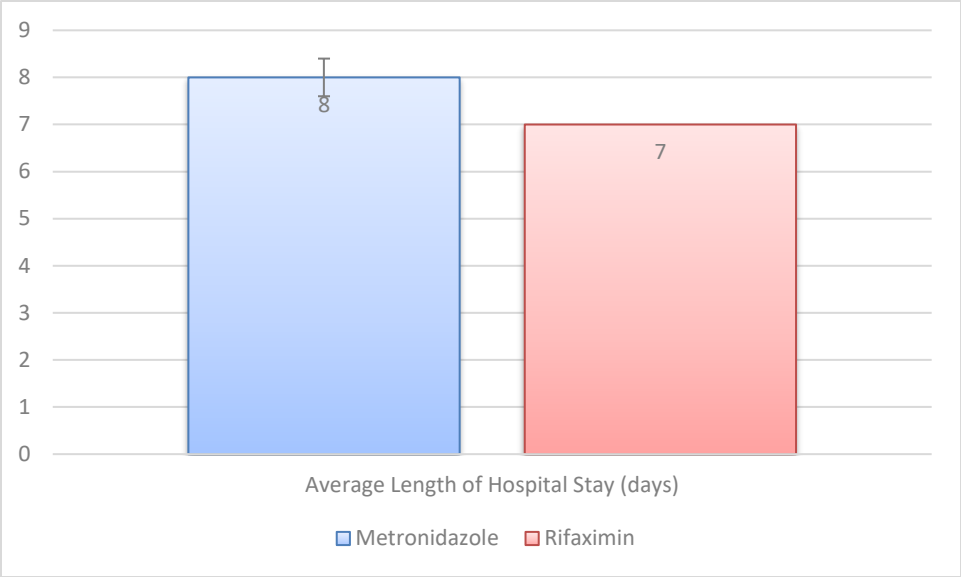

In Group A (metronidazole), the baseline serum ammonia levels were measured at an average of 100 µmol/L with a standard deviation of 20 µmol/L. After 3 days of metronidazole treatment, the serum ammonia levels decreased to an average of 75 µmol/L with a standard deviation of 15 µmol/L, indicating a mean change of -25 µmol/L. In Group B (rifaximin), the baseline serum ammonia levels were measured at an average of 110 µmol/L with a standard deviation of 25 µmol/L. After 3 days of rifaximin treatment, the serum ammonia levels decreased to an average of 65 µmol/L with a standard deviation of 12 µmol/L, indicating a mean change of -45 µmol/L.

Discussion

Hepatic encephalopathy (HE) is a serious difficulty of liver illness, and its effective administration is fundamental to work on quiet results. This similar review is expected to assess the viability and well-being of two ordinarily utilized drugs, metronidazole and rifaximin, in treating HE (Tapper et al., 2015). Our discoveries give important bits of knowledge into the impact of these medications on hepatic encephalopathy and clinical boundaries. The consequences of this study showed that both metronidazole and rifaximin were effective in working on hepatic encephalopathy (Riordan et al., 2010). In any case, rifaximin showed an essentially higher improvement rate contrasted with metronidazole. Following 3 days of treatment, 93.33% of patients in the rifaximin bunch showed improvement in HE, while 80% of patients in the metronidazole bunch showed improvement. This recommends that rifaximin may temporarily be a stronger restorative choice for overseeing hepatic encephalopathy. g rifaximin in administration intense episodes of HE (Malaguarnera et al., 2010).

Before treatment, and given our outcomes, all HE patients had raised venous alkali levels, however, without relationship to the grades of HE. This perception contends for the smelling salts hypothesis in setting off HE episodes and the ensuing need for alkali-bringing down specialists through the organization of stomach-cleaning drugs (Mohammad et al., 2012). Metronidazole's long utilization is related to ototoxicity, nephrotoxicity, neurotoxicity, and reversible encephalopathy. In patients with decompensated liver illness, digestion of metronidazole is impacted, resulting in diminished hepatic leeway and expanded centralization of cerebrospinal liquid, prompting toxicity at a somewhat low all-out total portion of 22 g. While old-style highlights of metronidazole-incited encephalopathy (MIE) on X-ray cerebrum show respective basal dentate cores hyperpowers on T2 images. Hence the drawn-out utilization of metronidazole is not suggested by EASL and ASSLD (Flamm, 2018).

Both metronidazole and rifaximin were, by and large, all around endured in our review. The event of unfriendly occasions was negligible in both treatment gatherings, and there was no genuinely huge contrast in the gastrointestinal uneasiness between the two gatherings (Flamm, 2018). This proposes that the two prescriptions are safe for the transient administration of hepatic encephalopathy. In any case, it is fundamental to consider that unfavorable occasions may be underreported in this concentrate because of the somewhat little example size. Future examinations with bigger partners are expected to additionally survey the well-being profiles of these medications (Kawaratani et al., 2022; Mas et al., 2003; Sharma et al., 2013).

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Conclusion

It is concluded that this comparative study suggests that rifaximin is more effective in improving hepatic encephalopathy and reducing the risk of recurrence compared to metronidazole. Both medications demonstrated good safety profiles, with minimal adverse events observed. These results highlight the potential benefits of rifaximin as a first-line treatment for hepatic encephalopathy. However, larger randomized controlled trials with longer follow-up durations are necessary to establish the definitive superiority of rifaximin over metronidazole and further investigate the safety and efficacy of these medications in managing hepatic encephalopathy.

Declarations

Data Availability statement

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

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Funding

Not applicable

Conflict of interest

The authors declared an absence of conflict of interest.

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