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Rifaximin and Metronidazole Fixed Dose Combination: New Treatment Option in the Management of Diarrhea

Arif A. Faruqui [a++*]

[a] *504-A Opp. KB Bhabha Hospital Waterfield Road, Bandra, West Mumbai-400050, India.*

Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

Background: Endemic infectious diarrhea is a widespread problem around the world, caused by a combination of viruses, bacteria, and parasites. While commonly used fluoroquinolone antibiotics are effective for specific types of acute diarrhea, they carry potential side effects.
Aim: To assess the effectiveness and tolerability of a fixed-dose combination of rifaximin and metronidazole as an alternative treatment approach for the management of acute diarrhea.
Study Design: A multicentre, open-label, non-comparative and non-randomized trial was conducted in 370 patients suffering from acute diarrhea due to various factors.
Methodology: Patients were given a tablet containing fixed-dose combination of 200 mg of rifaximin and 400 mg of metronidazole twice daily for 5 days. The primary outcomes evaluated were changes in the number of loose/watery stools, the presence of fever, nausea, vomiting, abdominal pain and gas/flatulence from baseline to day 5. A global assessment using a 3-point scale (Excellent/Good/Poor) was done by the investigators for efficacy and tolerability evaluation. Adverse drug reactions were monitored throughout the study period.

[++] *Clinical Pharmacologist and Associate Professor;*
**Corresponding author: E-mail: drfaruqui@gmail.com;*

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Results: After 5-day therapy, the average number of watery stools per day decreased significantly from 7.853 ± 3.773 to 0.766 ± 0.949 (*P* < *.001*). None of the patients experienced fever and vomiting, while few patients experienced nausea (0.31%), abdominal pain (0.31%), and gas/flatulence (0.93%) at the end of the study. According to the evaluation by the investigators, all patients reported good to excellent efficacy and tolerability.
Conclusions: The combination therapy of rifaximin and metronidazole is clinically effective and safe to treat acute diarrhea caused by different factors and can serve as a new treatment option for managing acute diarrhea.

Keywords: Acute diarrhea; fixed dose combination; metronidazole; mixed gastrointestinal infection; rifaximin.

1. INTRODUCTION

Diarrhoea is defined as “the passage of three or more loose or liquid stools per day (or a more frequent passage than is normal for the individual)” [1]. Acute diarrhea is frequently diagnosed in adults and poses a considerable health burden worldwide. Although in developing countries it is often recognized as one of the leading causes of childhood mortality, adult mortality from diarrhea is also prevalent, particularly during outbreaks. The high incidence of acute diarrhea among adults can be attributed to inadequate sanitation practices and unhygienic eating habits [2-3]. Contaminated food and water play an important role as primary sources of infection [4]. The primary causes of diarrhea are bacteria, viruses and parasites, whereas fungi play a minor role and are typically associated with individuals who have weakened immune systems. Bacterial pathogens such as *Shigella spp.*, *E. coli*, *Campylobacter spp.* and *Salmonella spp.* are commonly responsible for diarrhea [5]. Rotavirus, Norovirus and similar viruses (e.g Astrovirus) and Adenoviruses are common organisms causing gastrointestinal infections [1]. Protozoan parasites, including *Entamoeba histolytica* and *Giardia lamblia*, can lead to acute and chronic forms of diarrhea. These parasites are known to spread within specific geographic areas due to their widespread presence in water and food sources and their ability to withstand disinfection procedures and environmental factors [5].

In recent decades, the scientific community has reached a consensus on the most effective strategies to decrease the rate of occurrence, impact, and death from acute diarrhea. Several measures have been identified to decrease the incidence of diarrheal diseases, including ensuring access to clean water, proper management of human waste, promoting education on hygiene practices and improving food safety standards. From a therapeutic perspective, the implementation of oral rehydration therapy and intravenous rehydration therapy has been considered significant milestones in twentieth-century medicine. These treatment approaches, recommended since the 1970s, have played a crucial role in the management and treatment of acute diarrhea [6].

The primary objective of prescribing antibiotics for diarrheal diseases is to alleviate symptoms, shorten the duration of the disease, prevent the transmission of the infection by eliminating pathogens from the stool, and mitigate the risk of complications. The effectiveness of antibiotic therapy in reducing the symptoms and duration of diarrhea has been established firmly [5].

Rifaximin is a semi-synthetic derivative of rifamycin that exerts its action by binding to the β-subunit of bacterial DNA-dependent RNA polymerase. This mechanism leads to inhibition of the synthesis of bacterial RNA. Rifaximin demonstrates a broad spectrum of activity against both Gram-positive and Gram-negative anaerobic and aerobic bacteria. It exhibits effectiveness against a wide range of enteric bacterial pathogens, including *Clostridium difficile* and *Helicobacter pylori*. Rifaximin is minimally absorbed by the body and its antimicrobial properties are primarily targeted within the gastrointestinal tract, reducing the likelihood of antimicrobial resistance and systemic adverse effects. Rifaximin has been proven to be safe in various patient populations including children. Specifically, bacterial pathogens have demonstrated minimal capacity to develop resistance to rifaximin while under treatment. In cases where resistance did arise within the intestinal flora, it proved to be transient rather than stable. Furthermore, rifaximin has a minimal impact on both the Gram + and Gram - flora present in the colon [7].

Metronidazole, an antimicrobial medication, has been widely used in clinical practice for over 45 years. It has shown efficacy in the treatment of protozoal infections, including amoebiasis and giardiasis. The medication demonstrates strong effectiveness against gram-negative anaerobic bacteria like *Bacteroides fragilis* and gram-positive anaerobic bacteria such as *Clostridium difficile*. Metronidazole exhibits favorable pharmacokinetic and pharmacodynamic characteristics, strong effectiveness against pathogenic anaerobic bacteria, minimal adverse effects, and is considered a cost-effective option [8].

Based on the evidence presented, this study suggests that a fixed dose combination (FDC) of rifaximin and metronidazole could be a beneficial treatment choice for managing acute diarrhea and its related symptoms.

2. METHODOLOGY

2.1 Study Design and Patients

This study was a multicenter trial conducted in India, involving 370 patients across 37 clinics. It was open-label, noncomparative, and nonrandomized. Eligible participants included men and non-pregnant women aged over 18 years experiencing acute diarrhea. Exclusions criteria encompassed individuals with known or suspected hypersensitivity to any trial-related medications, dysentery, colitis, gastrointestinal bleeding, renal or liver failure, cardiac conditions, as well as pregnant or lactating women.

2.2 Treatment and its Duration

Patients were administered one tablet of Rifaxigyl-M, containing Rifaximin 200 mg and Metronidazole 400 mg, twice daily for a duration of 5 days.

2.3 Evaluation of the Primary Outcome Measure

The following parameters were evaluated at baseline, day 3 and day 5 of the study.

- Number of soft or watery stools
- Body temperature
- Nausea
- Vomiting
- Abdominal pain and
- Gas/flatulence

2.4 Evaluation of Secondary Outcome Measure

The study assessed efficacy and tolerability through investigator global assessment using a three-point scale (Excellent/Good/Poor). Adverse events were documented on a scale ranging from 1 to 3 (1 = mild, 2 = moderate, 3 = severe), and corresponding actions were recorded.

2.5 Statistical Analysis

Statistical analysis utilized the paired t-test to evaluate changes from baseline to day 5 for each parameter. Significance was set at a minimum of 95% confidence ($P < .05$ considered significant). All statistical analyses were conducted using GraphPad Prism 9 version 9.5.1.

3. RESULTS

The final analysis included a total of 320 patients, while 50 patients did not complete the follow-up. The recruited patients were in the 18 to 75 year age range (mean age 40.53±12.18). There is a significant reduction in the number of patients with fever by day 3, and by day 5, fever is completely resolved in all patients. Nausea also shows a significant decline over time, with only one patient still experiencing nausea by day 5. Vomiting is significantly reduced by day 3 and completely resolved by day 5. Abdominal pain decreases markedly by day 3, with only one patient still experiencing pain by day 5. Gas/flatulence also shows a significant decrease by day 3, with very few patients still experiencing it by day 5. Baseline and post-treatment clinical characteristics of patients assessed from September 2022 to March 2023 across 37 centres in India are shown in Table 1.

3.1 Number of Soft or Watery Stools

There was a statistically significant reduction in the number of daily stools observed with the rifaximin plus metronidazole fixed-dose combination on day 5 compared to baseline. The average number of stools per day decreased from 7.853 ± 3.773 to 0.766 ± 0.949 ($P < .001$) which are depicted in Fig. 1.

3.2 Other Parameters

Of 320 patients, 45.94% reported fever, 51.25% reported nausea, 51.56% reported vomiting, 65.31% reported abdominal pain and 51.88% reported gas/flatulence at baseline. None of the

Table 1. Baseline and Post-treatment Clinical Characteristics of patients assessed from September 2022 to March 2023 across 37 centres in India

Clinical symptoms	Number (%)		
	Baseline	Day 3	Day 5
Fever	147 (45.94%)	11 (3.44%)	0 (0%)
Nausea	164 (51.25%)	19 (5.94%)	1 (0.31%)
Vomiting	165 (51.56%)	19 (5.94%)	0 (0%)
Abdominal Pain	209 (65.31%)	28 (8.75%)	1 (0.31%)
Gas/Flatulence	166 (51.88%)	23 (7.19%)	3 (0.94%)

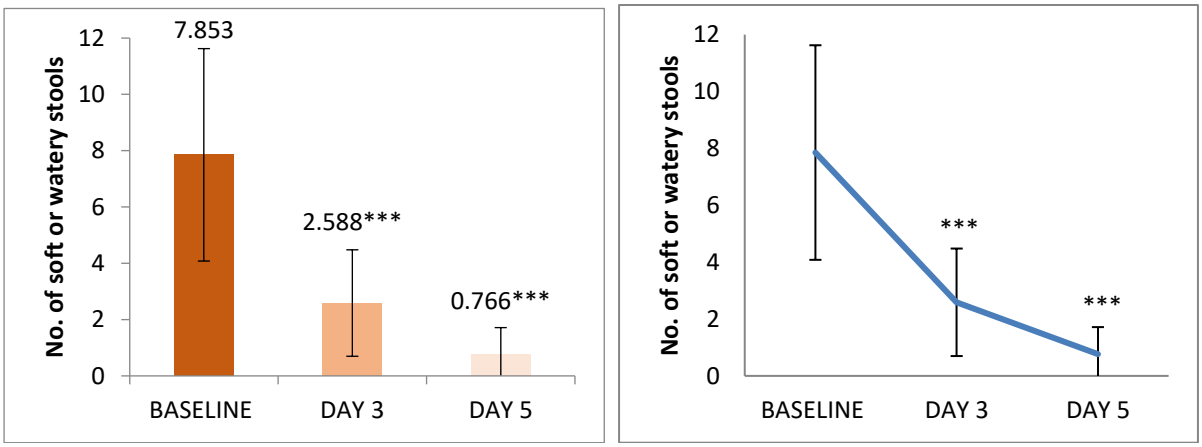

Fig. 1. Mean reduction in the number of watery stools from 7.853 ± 3.773 to 0.766 ± 0.949 assessed across 37 centres in India. ****P < .001*

patients reported fever or vomiting at the end of the study. Few patients reported nausea (0.31%), abdominal pain (0.31%), and gas/flatulence (0.94%) at the end of the study.

3.3 Safety Evaluation

Gastritis occurred in 2.81% of patients, while nausea and metallic taste were reported in 2.81% and 12.5% of patients, respectively. There were no serious adverse events that necessitated patient withdrawal from the study.

3.4 Global Assessment of Efficacy and Tolerability

As per the investigators' assessment of the rifaximin + metronidazole fixed-dose combination's efficacy, 75.31% of patients reported excellent efficacy, and 24.69% reported good efficacy. In terms of tolerability, 80% of patients reported excellent tolerability, while 20% reported good tolerability according to the investigators' assessment.

4. DISCUSSION

Diarrhea commonly stems from gastrointestinal infections with diverse causes. To effectively treat these complex infections, a combination therapy involving a broad-spectrum antibiotic and an antiprotozoal medication is essential.

Rifaximin has demonstrated efficacy and safety across various clinical studies and systematic reviews involving conditions such as traveler's diarrhea [9], small intestinal bacterial overgrowth (SIBO) [10], diarrhea-predominant irritable bowel syndrome [11], and hepatic encephalopathy [12]. It has also shown promise in managing Clostridium difficile infection (CDI), particularly in cases of recurrence [13]. Strong evidence supports its use as a prophylactic treatment for travelers' diarrhea, especially in individuals at heightened risk of severe complications from acute infectious diarrhea [14]. Because rifaximin is minimally absorbed, it avoids systemic drug interactions and boasts an excellent safety profile with limited potential for side effects. Thus, this gut-selective antibiotic represents a promising option for treating acute infectious diarrhea and for chemoprophylaxis in travellers [15].

In cases of mixed infections, protozoa, including *Giardia lamblia*, *Entamoeba histolytica*, and *Cryptosporidium spp.*, were found most frequently in 73% of patients [16]. Metronidazole remains effective against protozoal infections such as trichomoniasis, amoebiasis, and giardiasis [8], making it a suitable complement to rifaximin in the treatment of mixed infections. Another study [17] assessed the combination of rifaximin and metronidazole in patients with acute diarrhea, concluding that this combination significantly reduces the frequency of watery stools and associated symptoms.

In this study, the combination of rifaximin and metronidazole markedly decreased the frequency of loose or watery stools. By the study's conclusion, all patients were free of fever. Symptoms commonly associated with diarrhea, such as nausea, vomiting, abdominal pain, and gas/flatulence, were significantly alleviated. None of the participants withdrew from the study due to adverse events, and minor occurrences of gastritis, nausea, and metallic taste were noted. Therefore, based on existing clinical evidence and the findings of this study, rifaximin combined with metronidazole emerges as a safe and effective treatment option for managing acute diarrhea caused by mixed infections.

Limitation of study: A significant limitation of this study is the absence of stool examinations for patients. Stool examinations were omitted due to the mixed nature of gastrointestinal infections and the additional cost burden, especially considering the low per capita income in many households. Routine stool examinations could have provided more objective study outcomes, particularly in excluding diarrhea caused solely by viral infections, which often resolve without specific treatment.

5. CONCLUSION

Acute diarrhea poses a substantial challenge in India. In the quest for a more effective and safer treatment, the fixed-dose combination of rifaximin and metronidazole emerges as a promising addition. This combination therapy has demonstrated significant reductions in diarrhea frequency and associated symptoms, proving highly effective and well-tolerated. Thus, the fixed-dose combination of rifaximin and metronidazole stands out as an innovative, safe, and effective option for managing episodes of acute diarrhea.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Authors hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT

It is not applicable.

ETHICAL APPROVAL

This is an observational study. The study was conducted after approval of the drug by the state FDA.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. National Guidelines for Infection Prevention and Control in Healthcare Facilities. Ministry of Health and Family Welfare, Government of India Website. [Published Jan 2020; cited Jun 13, 2023.
Available:https://www.mohfw.gov.in/pdf/National%20Guidelines%20for%20IPC%20in%20 HCF%20-%20final%281%29.pdf.
2. Schiller LR, Pardi DS, Sellin JH. Chronic diarrhea: Diagnosis and management. Clinical Gastroenterology and Hepatology. 2017 Feb 1;15(2):182-93.
3. D'amico F, Baumgart DC, Danese S, Peyrin-Biroulet L. Diarrhea during COVID-19 infection: pathogenesis, epidemiology, prevention, and management. Clinical Gastroenterology and hepatology. 2020 Jul 1;18(8):1663-72.
4. Manatsathit S, Dupont HL, Farthing M, et al. Working Party of the Program Committ of the Bangkok World Congress of Gastroenterology 2002. Guideline for the management of acute diarrhea in adults. J

Gastroenterol Hepatol. 2002 Feb;17 Suppl:S54-71.
5. Herbert L DuPont. Community acquired diarrheal disease in western countries: Application of Nonabsorbable oral antibiotic therapy. Adv Stud Med. 2003;3(10A):S945-S950.
6. Brandt KG, Castro Antunes MM, Silva GA. Acute diarrhea: evidence-based management. J Pediatr (Rio J). 2015 Nov-Dec;91(6 Suppl 1):S36-43.
7. Huang DB, DuPont HL. Rifaximin--a novel antimicrobial for enteric infections. J Infect. 2005 Feb;50(2):97-106.
8. Löfmark S, Edlund C, Nord CE. Metronidazole is still the drug of choice for treatment of anaerobic infections. Clin Infect Dis. 2010 Jan 1;50 Suppl 1:S16-23.
9. Layer P, Andresen V. Review article: rifaximin, a minimally absorbed oral antibacterial, for the treatment of travellers' diarrhoea. Aliment Pharmacol Ther. 2010 Jun;31(11):1155-64.
10. Wang J, Zhang L, Hou X. Efficacy of rifaximin in treating with small intestine bacterial overgrowth: a systematic review and meta-analysis. Expert Rev Gastroenterol Hepatol. 2021 Dec;15(12):1385-1399.
11. Chang C. Short-course therapy for diarrhea-predominant irritable bowel syndrome: understanding the mechanism, impact on gut microbiota, and safety and tolerability of rifaximin. Clin Exp Gastroenterol. 2018 Sep 24;11:335-345.
12. Hudson M, Schuchmann M. Long-term management of hepatic encephalopathy with lactulose and/or rifaximin: A review of the evidence. Eur J Gastroenterol Hepatol. 2019 Apr;31(4):434-450.
13. Ng QX, Loke W, Foo NX, Mo Y, Yeo WS, Soh AYS. A systematic review of the use of rifaximin for Clostridium difficile infections. Anaerobe. 2019 Feb;55: 35-39.
14. Ng QX, Ho CYX, Shin D, Venkatanarayanan N, Chan HW. A meta-analysis of the use of rifaximin to prevent travellers' diarrhoea. J Travel Med. 2017 Sep 1;24(5).
15. Faruqui AA, Shaikh ST, Ali F. Post Marketing Observational Study of Fixed Dose Combination of Rifaximin and Metronidazole in The Management of Acute Diarrhea. Indonesian Journal of Gastroenterology, Hepatology & Digestive Endoscopy. 2023 Aug 1;24(2).
16. Lindsay B, Ramamurthy T, Sen Gupta S, Takeda Y, Rajendran K, Nair GB, Stine OC. Diarrheagenic pathogens in polymicrobial infections. Emerg Infect Dis. 2011 Apr;17(4):606-11.
17. Faruqui AA. Evaluation of efficacy and tolerability of fixed dose combination of rifaximin and metronidazole in the management of acute diarrhea. The Indonesian Journal of Gastroenterology, Hepatology, and Digestive Endoscopy. 2023 Nov 24;24(2):122–6.

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