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Research Article

A Novel Approach to Diarrhea Management The Fixed Dosage Combination of Rifaximin and Metronidazole

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Abstract

Background: Worldwide, endemic infectious diarrhea is a common issue brought on by a confluence of bacteria, viruses, and parasites. Fluoroquinolone antibiotics, which are often used, have the potential to cause adverse effects even though they are beneficial for certain types of severe diarrhea. **Goal:** To evaluate the efficacy and tolerability of a fixed-dose combination of metronidazole and rifaximin as a substitute therapeutic strategy for the treatment of acute diarrhea. **study design:** 370 individuals with acute diarrhea caused by a variety of reasons participated in a multicenter, open-label, non-comparative, and non-randomized study. **Methodology:** For five days, patients received a pill that included a fixed-dose combination of 400 mg of metronidazole and 200 mg of rifaximin twice a day. Changes in the frequency of loose or watery stools, fever, nausea, vomiting, stomach pain, and gas/flatulence from day 1 to day 5 were the main outcomes assessed. In order to evaluate efficacy and tolerability, the researchers conducted a worldwide assessment utilizing a 3-point rating system (Excellent, Good, and Poor). Throughout the course of the trial, adverse medication reactions were tracked. **Results:** Following a 5-day treatment, the mean frequency of watery stools per day dramatically diminished from 7.853 ± 3.773 to 0.766 ± 0.949 ($P < .001$). No participants exhibited fever or vomiting, whereas a small number reported nausea (0.31%), abdominal pain (0.31%), and gas/flatulence (0.93%) by the conclusion of the trial. The investigators' assessment indicated that all patients reported good to exceptional effectiveness and tolerability. **Conclusion:** The combination therapy of rifaximin and metronidazole is both clinically efficacious and safe for treating acute diarrhea resulting from various etiologies, presenting a novel treatment option for its management.

1. Introduction

As per the definition, diarrhea is "the passage of three or more loose or liquid stools per day (or a more frequent passage than is typical 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].

A semi-synthetic derivative of rifamycin, rifaximin works by attaching itself to the bacterial DNA-dependent RNA polymerase's β-subunit. This process results in the suppression of bacterial RNA production. Rifaximin exhibits a wide range of activity against aerobic and anaerobic bacteria that are Gram-positive and Gram-negative. It works well against Helicobacter pylori and Clostridium difficile, among other intestinal bacterial pathogens. Since the body absorbs rifaximin very little and its antimicrobial effects are mostly seen in the gastrointestinal tract, it is less likely to cause systemic side effects and antimicrobial resistance. Children are among the patient groups for whom Rifaximin has been shown to be safe. In particular, it has been shown that bacterial infections have little ability to become resistant to rifaximin during treatment. When resistance did develop in the intestinal flora, it was temporary rather than permanent. Additionally, rifaximin has little effect on the colon's Gram + and Gram - flora [7].

For more than 45 years, the antibacterial drug metronidazole has been utilized extensively in therapeutic settings. It has demonstrated effectiveness in treating protozoal illnesses, such as giardiasis and amoebiasis. Gram-positive anaerobic bacteria like Clostridium difficile and gram-negative anaerobic bacteria like Bacteroides fragilis are both effectively combatted by the drug. Metronidazole has good pharmacokinetic and pharmacodynamic properties, is highly effective against harmful anaerobic bacteria, has few side effects, and is regarded as an affordable alternative [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

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.

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.

Evaluation of the Primary Outcome Measure

The following parameters were evaluated at baseline, day 3 and day 5 of the study.
- The quantity of limp or watery stools
- The body temperature
- Nausea
- Vomiting
- Abdominal pain and discomfort
- Gas/flatulence

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.

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,

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%)

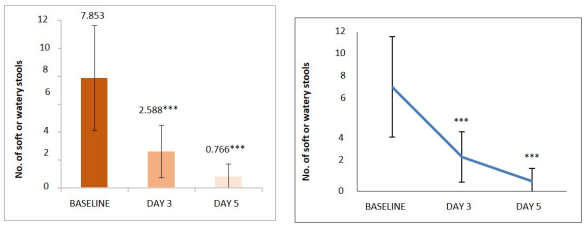

Figure 1: Mean reduction in the number of watery stools from 7.853 $\pm$ 3.773 to 0.766 $\pm$ 0.949 assessed across 37 centres in India. ***P $<$ .001

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.

Number of Soft or Watery Stools

When compared to baseline, the number of daily stools was statistically significantly lower on day 5 when using the rifaximin + metronidazole fixed-dose combination. As seen in Figure 1, the average daily stool count dropped from 7.853 $\pm$ 3.773 to 0.766 $\pm$ 0.949 (P $<$ 001).

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 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.

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.

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.

In numerous clinical trials and systematic reviews, Rifaximin has proven to be effective and safe in treating disorders such hepatic encephalopathy [9], diarrhea-predominant irritable bowel syndrome [10], small intestinal bacterial overgrowth (SIBO) [11], and traveler's diarrhea [12]. Additionally, it has demonstrated potential in the treatment of Clostridium difficile infection (CDI), especially when it recurs [13]. Its use as a preventative therapy for travelers' diarrhea is well-supported by evidence, particularly for those who are more susceptible to serious consequences from acute infectious diarrhea [14]. Rifaximin has a great safety profile with little chance of adverse effects and is minimally absorbed, preventing systemic medication interactions. Therefore, this gut-selective antibiotic is a promising treatment for travelers' chemoprophylaxis and acute infectious diarrhea [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.

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