PACIFIC JOURNAL OF MEDICAL SCIENCES

{Formerly: Medical Sciences Bulletin}

ISSN: 2072 – 1625

Pac. J. Med. Sci. (PJMS)

www.pacjmedsci1625.com. Email: managingeditorpjms1625@gmail.com.

POST MARKETING OBSERVATIONAL STUDY OF FIXED DOSE COMBINATION OF RIFAXIMIN AND METRONIDAZOLE IN THE MANAGEMENT OF ACUTE DIARRHEA IN CHILDREN

Running title: Rifaximin and Metronidazole FDC in Children

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ABSTRACT

Acute diarrhea is a frequent illness in children, especially in developing nations, posing risks of dehydration, malnutrition, and even death. Recently, there's been rising interest in Rifaximin and Metronidazole Fixed Dose Combination (FDC) as a treatment option for pediatric acute diarrhea. The aim of this study was to evaluate the efficiency and tolerability of rifaximin and metronidazole fixed-dose combination in the management of acute diarrhea in children. This was a multicenter, open-label, non-comparative, and non-randomized trial that enrolled 80 patients (age <18 years) experiencing acute diarrhea caused by various factors. This observational study was conducted post-approval of drugs by state Food and Drug Administration (FDA), therefore informed consent and ethics approval were not mandatory. Patients received suspension containing 100mg rifaximin and 200mg metronidazole per 5ml, twice daily for 5 days based on body weight. The primary endpoint assessed was change in frequency of loose/watery stools, fever, nausea, vomiting, abdominal pain, and gas/flatus from baseline to day 5. Statistical analysis using the 'paired t-test' was performed. A total of 64 patients were included in the final analysis with 16 patients lost to follow-up. The average number of watery stools per day decreased significantly from 7.0±1.49 to 2.0±0.66 ($P < 0.001$) after a 5-day therapy. None of the patients experienced fever, nausea, vomiting, abdominal pain or gas/flatus at the end of the study. Rifaximin and Metronidazole FDC demonstrates significant reduction in frequency of watery stools and alleviation of associated symptoms, establishing it as a clinically effective and safe choice for empirically managing acute diarrhea in children stemming from diverse causes.

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

Submitted: April; Accepted: May 2025

INTRODUCTION

Diarrhea is defined as the passage of three or more loose or liquid stools per day and is a leading cause of child mortality and morbidity worldwide, largely due to contaminated food and water [1]. It results in approximately 443,832 deaths annually among children under five and 50,851 among those aged 5 to 9. Access to safe drinking water, sanitation, and hygiene can significantly reduce cases. There are nearly 1.7

billion reported cases of childhood diarrhea each year [1], primarily caused by viruses, bacteria, and parasites. Common bacterial culprits include E. coli, Shigella spp., Salmonella spp., and Campylobacter spp., while Giardia and Entamoeba are notable protozoan parasites [2]. Effective strategies to combat diarrhea include improving water quality, sanitation, hygiene education, and food safety. Treatments like oral and intravenous rehydration therapy have been crucial since the 1970s, and antibiotics are used to alleviate symptoms, reduce illness duration, and prevent transmission [3].

Rifaximin, a semi-synthetic derivative of rifamycin, functions by binding to the β-subunit of bacterial DNA-dependent RNA polymerase, thereby inhibiting bacterial RNA synthesis. This mechanism gives rifaximin a broad spectrum of activity against aerobic and anaerobic Gram-positive and Gram-negative bacteria [4]. It effectively targets enteric pathogens such as Clostridium difficile and Helicobacter pylori. Due to its limited systemic absorption, rifaximin primarily exerts its antimicrobial effects in the gastrointestinal tract, which reduces the risk of developing antimicrobial resistance and systemic side effects. Rifaximin is well-tolerated across various patient groups, including young children. Notably, bacterial resistance to rifaximin during treatment has shown minimal potential and, if present, is typically unstable within the intestinal flora. Additionally, rifaximin minimally impacts both Gram-positive and Gram-negative flora in the colon [4].

Metronidazole is an antimicrobial agent with a longstanding history in clinical use spanning over 45 years. It has proven effective in treating protozoal infections like amoebiasis and giardiasis. The drug demonstrates potent activity against gram-negative anaerobic bacteria such as Bacteroides fragilis and gram-positive anaerobic bacteria like Clostridium difficile. Metronidazole is recognized for its favourable pharmacokinetic and pharmacodynamic profiles, robust efficacy against anaerobic pathogens, minimal adverse effects, and cost-effectiveness [5]. Based on the evidence presented, the present study suggests that a FDC of rifaximin and metronidazole is a promising treatment option for effectively managing acute diarrhea and its related symptoms in children.

METHODOLOGY

Study design and Patients

This study, conducted in 8 clinics across diverse regions of India, was an open-label, non-comparative, non-randomized, multicenter trial involving 80 patients. Children (<18 years) were eligible if they were experiencing acute diarrhea, while exclusion criteria encompassed known or suspected hypersensitivity to trial-related medications, dysentery, colitis, gastrointestinal bleeding, renal or liver failure, cardiac conditions and pregnancy or lactation. Final analysis comprised 64 patients, with 16 lost to follow-up. The enrolled patients ranged in age from 3 to 15 years, with a mean age of 6.75 ± 2.81 years.

Ethical Considerations:

This was an observational study. The study was conducted after approval of the drug by the state FDA; therefore, ethical approval was not mandatory.

Treatment and duration of treatment:

Patients were administered Rifaxigyl-M suspension (Medley Pharmaceuticals Ltd.) containing Rifaximin 100 mg and Metronidazole 200 mg per 5 ml twice daily for 5 days. Dosage was based on their body weight at a dose of Rifaximin 10 mg/kg/day and Metronidazole 20 mg/kg/day.

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/flatus.

Evaluation of the secondary outcome measure

Global assessment by the investigator on a three-point scale marked as Excellent/Good/Poor was used for efficacy and tolerability evaluation. Adverse events were recorded and the action taken was documented.

Statistical analysis

Statistical analysis was performed using the 'paired t test' for number of soft or watery stools per day to assess the change from baseline on day 5. The minimum level of significance was fixed at the 95% confidence limit and $P < 0.05$ was considered significant. All statistical analysis was performed using Graph Pad Prism 9 version 9.5.1.

RESULTS

A total of 64 patients were included for final analysis, with 16 patients lost to follow-up. The enrolled patients ranged in age from 3 to 15 years, with a mean age of 6.75 ± 2.81 years. Baseline and post-treatment clinical symptoms are shown in Table 1.

Number of soft or watery stools:

The number of stools per day was recorded at the start and end of the trial. Statistically significant reduction in the number of bowel movements was reported with rifaximin plus metronidazole fixed dose combination compared to baseline. The number of stools per day reduced from 7.0±1.49 to 2.0±0.66 ($P < 0.001$) which are depicted in Figure 1.

Other Parameters:

Of 64 patients, 35.93% reported fever, 23.43% reported nausea, 48.43% reported vomiting, 45.31% reported abdominal pain and 23.43% reported gas/flatus at baseline. None of the patients reported fever, nausea, vomiting, abdominal pain or gas/flatus at the end (day 5) of the trial.

Safety Evaluation

No adverse events were reported that led to the withdrawal of a patient from the study.

Global assessment of efficacy and tolerability:

According to investigators assessment of efficacy and tolerability of Rifaximin and Metronidazole FDC, 87.5% of the patients reported excellent and 12.5% of the patients reported good efficacy as well as tolerability.

DISCUSSION

Diarrhea commonly stems from complex gastrointestinal infections with diverse causes. Effective management of these infections often requires a combination therapy that includes a broad-spectrum antibiotic and an antiprotozoal medication. Even today, cost remains a significant factor, leading doctors to avoid frequent stool examinations. Instead, they often recommend empirical treatment targeting both bacteria and protozoa, common culprits due to prevalent unhygienic conditions in the country. This approach not only cuts down on therapy expenses but also minimizes the days of work missed and subsequent loss of wages due to diarrhea.

Rifaximin has shown efficacy and tolerability in several clinical studies and systematic reviews that included patients with traveler's diarrhea [6], small intestinal bacterial overgrowth (SIBO) [7], diarrhea-predominant irritable bowel syndrome [8] and hepatic encephalopathy [9]. Rifaximin has also demonstrated promise in treating Clostridium difficile infection (CDI), particularly in cases of recurrent CDI [10]. Good evidence supports rifaximin use as a chemoprophylactic agent in traveler's diarrhea, especially in people at high risk of severe complications from acute infectious diarrhea [11]. A short treatment course (3 days on average) with rifaximin oral suspension when compared to neomycin and bacitracin combination yielded highly satisfactory results in children suffering from severe episodes of bacterial diarrhea [12]. Similarly, another study compared oral pediatric suspension of rifaximin with paromomycin for the oral treatment of pediatric infectious diarrhea. The study concluded that rifaximin rapidly exerts its antimicrobial action, shows very good clinical effectiveness and can be used with complete safety, particularly for the treatment of younger children [13].

In cases of mixed infections, 73% of patients were predominantly diagnosed with protozoa such as Giardia lamblia, Entamoeba histolytica, and Cryptosporidium spp. [14]. Metronidazole remains effective against protozoal infections, supporting its use in treating conditions like trichomoniasis, amoebiasis, and giardiasis [5]. Therefore, it should be considered as a complement to rifaximin in the treatment of mixed infections. A similar study that evaluated the combination of rifaximin and metronidazole in adult patients with acute diarrhea concluded that the combination significantly reduces diarrheal episodes and associated symptoms [15]. A study reported by Gawronska et al showed similar effectiveness of metronidazole and rifaximin treatments for Clostridium difficile infection in pediatric patients (age between 12 and 18 years) with IBD [16].

In the present study, the FDC of rifaximin and metronidazole significantly reduced the number of soft or watery stools. At the end of the study, none of the patients reported fever, nausea, vomiting, abdominal pain or flatus. None of the patients withdrew from the study due to adverse events. Thus, based on clinical studies literature and present clinical data, rifaximin and metronidazole FDC suspension is a safe and effective treatment option for the empirical management of acute diarrhea in pediatric patients due to mixed infections.

Limitation of the study:

While the combination showed a notably positive response, a major limitation of the study was the absence of stool examinations for patients. Stool examinations were omitted due to the common mixed nature of gastrointestinal infections, and the additional cost to patients, particularly significant in households with low per capita income. Conducting routine stool examinations could have provided more unbiased study results, particularly in ruling out diarrhea caused by exclusive viral infections, which are often self-limiting illnesses.

CONCLUSION

Addressing acute diarrhea in children poses a substantial challenge in India. Seeking a more effective and safer treatment approach, the fixed-dose combination of rifaximin and metronidazole suspension emerges as a promising addition to the therapeutic arsenal. This combined therapy has demonstrated a significant decrease in diarrhea frequency and associated symptoms, showcasing outstanding efficacy and tolerability. Consequently, the FDC of rifaximin and metronidazole stands out as an innovative, safe and efficacious treatment option for managing episodes of acute diarrhea in children.

Table 1: Baseline and Post-treatment Clinical Symptoms			
Clinical symptoms	Number (%)		
	Baseline	Day 3	Day 5
Fever	23 (35.93%)	4 (6.25%)	0 (0%)
Nausea	15 (23.43%)	2 (3.125%)	0 (0%)
Vomiting	31 (48.43%)	8 (12.5%)	0 (0%)
Abdominal Pain	29 (45.31%)	8 (12.5%)	0 (0%)
Gas/Flatus	15 (23.43%)	6 (9.37%)	0 (0%)

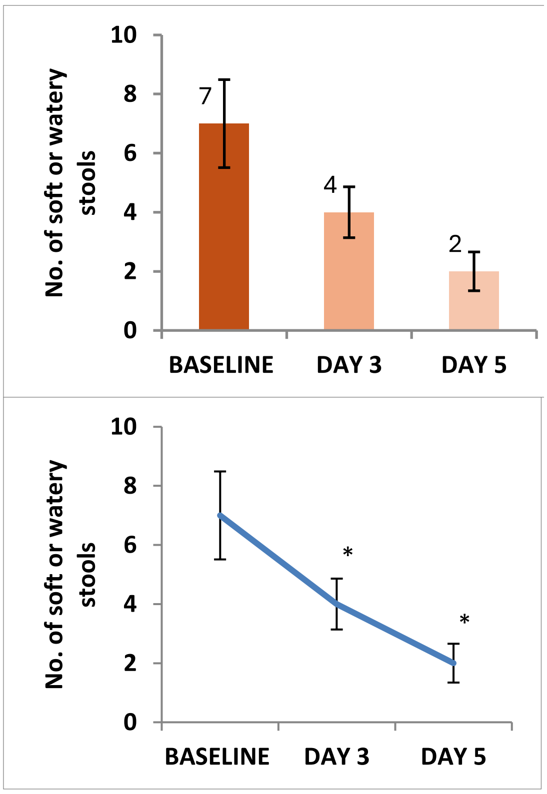

Figure 1: Mean reduction in the number of watery stools. *P < 0.001

ACKNOWLEDGEMENT

Authors acknowledge the contribution of Mr. Rafique Sheikh, M. Pharm (Pharmacology) in doing literature search and help in the preparation of the manuscript.

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