3. Hapsari PF, Putri L, Rahardja C, Utari A, Syam AF. Prevalence of gastroesophageal reflux disease and its risk factor in rural area. Indones J Gastroenterol Hepatol Dig Endosc 2017;18:9–14.
4. Clarrett DM, Hachem C. Gastroesophageal reflux disease (GERD). Mo Med 2018;115:214–8.
5. Tarigan R, Pratomo B. Analisis faktor risiko gastroesofageal refluks di RSUD Saiful Anwar Malang. J Penyakit Dalam Indones 2019;6:78.
6. Scapaticci S, Neri CR, Marseglia GL, Staiano A, Chiarelli F, Verduci E. The impact of the COVID-19 pandemic on lifestyle behaviors in children and adolescents : an international overview. Ital J Pediatr 2022;1–17.
7. Alhuzaim WM, Alotaibi AT, Alruwaybiah HA, Alharthi NS, Alzahrani SA, AlDera NM, et al. The prevalence and risk factors of GERD in the Kingdom of Saudi Arabia and the impact of COVID-19 pandemic. Int Res J Public Environ Heal 2021;8:284–92.
8. Groff A, Kavanaugh M, Ramgobin D, McClafferty B, Aggarwal CS, Golamari R, et al. Gastrointestinal manifestations of COVID-19: a review of what we know. Ochsner J 2021;21:177–80.
9. Zeng W, Qi K, Ye M, Zheng L, Liu X, Hu S, et al. Gastrointestinal symptoms are associated with severity of coronavirus disease 2019: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol 2022;34:168–76.
10. Lukito A, Widyaningrum K. Why do inpatient visits decrease during the COVID-19 pandemic? A case study in hospital, Malang regency. Jurnal Kedokteran Brawijaya 2021;31:11–5.
11. Zhao Y, Encinosa W. Gastroesophageal reflux disease (GERD) hospitalizations in 1998 and 2005. Healthc Cost Util Proj 2008;x:2340–8.
12. Syam AF, Hapsari PF, Makmun D. The prevalence and risk factors of GERD among Indonesian medical doctors. Makara J Heal Res 2016;20:35–40.
13. Sakti P, Mustika S. Analisis faktor risiko gastro-esophageal reflux disease di era pandemi COVID-19 pada mahasiswa Program Pendidikan Dokter Spesialis Fakultas Kedokteran Universitas Brawijaya. J Penyakit Dalam Indones 2022;9:164–70.
14. Gosal D, Santoso RE, Firmansyah Y. Association between gastroesophageal reflux disease-questionnaire factors and gastroesophageal reflux disease incidence at Kardinah general hospital inpatient wards. Int J Adv Med Sci 2021;8:152–7.
15. Yaseri HF. Gender is a risk factor in patients with gastroesophageal reflux disease. Med J Islan Repub Iran 2017;2017:8–10.
16. Wang H, Leena KB, Plymoth A, Hergens M, Yin L. Prevalence of gastro-esophageal reflux disease and its risk factors in a community- based population in southern India. BMC Gastroenterol 2016;16:1–6.
17. Ronkainen J, Aro P, Storskrubb TOM, Lind T, Bolling-sternevald E, Vieth M, et al. High prevalence of gastroesophageal reflux symptoms and esophagitis with or without symptoms in the general adult Swedish population : a Kalixanda study report. Scand J Gastroenterol 2005;40:275–85.
18. Suryadinata RV, Wirjatmadi B, Adriani M, Lorensia A. Effect of age and weight on physical activity. J Public Health Res 2020;9:187–90.
19. Watson KB, Carlson SA, Gunn JP, Galuska DA, Connor AO, Greenlund KJ, et al. Physical inactivity among adults aged 50 years and older —. MMWR Morb Mortal Wkly Rep 2016;65:954–8.
20. Thrift AP, Kramer JR, Qureshi Z, Richardson PA, El-Serag HB. Age at onset of GERD symptoms predicts risk of Barrett's esophagus. Am J Gastroenterol 2014;2013:915–22.
21. Altwigry AM, Almutairi MS, Ahmed M. Gastroesophageal reflux disease prevalence among school teachers of Saudi Arabia and its impact on their daily life activities. Int J Health Sci (Qassim) 2017;11:59–64.
22. Sharma PK, Ahuja V. Prevalence, severity, and risk factors of symptomatic gastroesophageal reflux disease among employees of a large hospital in Northern India. Indian J Gastroenterol 2011;30:128–34.
23. Ramadani AN, Sartika D, Herawaty H. Increase in unemployment rates during the COVID-19 pandemic. Jur Ilm Adm Manaj 2022;15:111–20.
24. Sharma A, Praveen C, Sharma K. ScienceDirect prevalence and the risk factors of gastro-esophageal reflux disease in medical students. Med J Armed Forces India 2018;74:250–4.
25. Wala SFW. The psychological aspects of home-makers and women during pandemic. Intech 2021;11:13.
26. Ping MF, Natalia E, Hurai R. The impact of COVID-19 to the mental health of housewives and the adaptation process from a cultural perspective. Malaysian J Nurs 2022;13:71–6.
27. Giuntella O, Hyde K, Saccardo S, Sadoff S. Lifestyle and mental health disruptions during COVID-19. Proc Natl Acad Sci 2021;118:1–9.
28. Park K, Kim A, Yang M, Lim S, Id JP. Impact of the COVID-19 pandemic on the lifestyle, mental health, and quality of life of adults in South Korea. Plos One 2021;16:1–13.
29. Richter JE, Rubenstein JH. Presentation and epidemiology of gastroesophageal. Gastroenterology 2018;154:267–76.
30. Chen CL, Hsu PI. Current advances in the diagnosis and treatment of nonerosive reflux disease. Gastroenterol Res Pract. 2013;2013:653989.
31. Kellerman R, Kintanar T. Gastroesophageal reflux disease. Prim Care - Clin Off Pract 2017;44:561–73.
32. Jameson JL, Fauci A, Kasper DL, Hauser SL, Longo DL, Loscalzo J. Harrison's Principle of Internal Medicine. 20th ed. New York: McGraw-Hill Education 2018:XX.p.5–24.

Post Marketing Observational Study of Fixed Dose Combination of Rifaximin and Metronidazole in The Management of Acute Diarrhea

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ABSTRACT

Background: *Infectious diarrhea is endemic in many parts of the world. It is generally mixed in etiology involving viruses, bacteria, and parasites. Antibiotics belonging to fluoroquinolones class are most commonly used but are beneficial only in certain types of acute diarrhea with side effects like tendinopathy, arthropathy, neuropathy, arrhythmia, hypoglycemia, and hyperglycemia. Rifaximin with its unique mechanism, along with established metronidazole is proposed as a treatment option for acute diarrhea caused due to mixed gastrointestinal infections. This study aims to evaluate the efficacy and tolerability of a fixed-dose combination of rifaximin and metronidazole in the empirical management of acute diarrhea.*

Method: *An open-label, non-comparative, non-randomized, multicenter trial was conducted on 238 patients presenting with acute diarrheal episodes involving various etiologies. Since this is an observational study and was conducted post-approval of the drug by the state FDA; informed consent and ethics approval was not mandatory. Patients were given fixed dose combination tablet containing rifaximin 200 mg and metronidazole 400 mg twice a day for 5 days. Primary outcomes were a change from baseline in the number of soft or watery stools, fever, nausea, vomiting, abdominal pain, and gas/flatus at day 5.*

Results: *In the final analysis, 150 patients were included, as 88 patients were lost to follow-up. After 5 days of therapy, the mean number of watery stools per day was reduced from 7.133 ± 2.055 to 0.733 ± 0.833 ($p < 0.0001$). Side effects complaints such as gastritis (5.33%), nausea (10.66%), and metallic taste (3.33%) were reported.*

Conclusion: *A combination of rifaximin and metronidazole significantly reduces the number of watery stools and associated symptoms and is a clinically effective and safe option in the empirical management of acute diarrhea of various etiologies.*

Keywords: *acute diarrhea, mixed gastrointestinal infection, rifaximin, metronidazole*

ABSTRAK

Latar Belakang: *Diare akibat infeksi merupakan penyakit endemik di beberapa negara di dunia. Penyebab dari infeksi tersebut dapat beragam hingga multipatogen seperti virus, bakteri, dan parasite. Antibiotik golongan flouroquinolone merupakan salah satu yang sering dipakai untuk kasus diare akut, akan tetapi memiliki beberapa efek samping seperti tendinopati, artropati, neuropati, aritmia, hipoglikemia, dan hiperglikemia. Rifaximin diketahui memiliki mekanisme yang unik. Rifaximin bersama dengan metronidazole diajukan sebagai pilihan terapi untuk diare akut akibat infeksi campuran. Penelitian ini bertujuan untuk mengevaluasi efikasi dan tolerabilitas dari obat kombinasi dosis tetap dari rifaximin dan metronidazole sebagai terapi empiric diare akut*

Metode*: Studi open label, non-komparatif, tidak terandomisasi, multisenter ini dilakukan dengan melibatkan 238 pasien dengan diare akut yang diakibatkan berbagai etiologi. Karena studi ini merupakan studi observasional dan dilakukan menggunakan obat yang telah disetujui oleh badan FDA setempat, persetujuan pasien dan etik tidak diwajibkan. Pasien diberikan obat kombinasi dosis tetap dari rifaximin 200 mg dan metronidazole 400 mg dua kali sehari selama 5 hari. Keluaran utama dari studi ini adalah perubahan jumlah bab cair, demam, mual, muntah, nyeri perut, dan flatus pada hari kelima pengobatan dibandingkan dengan saat pertama kali berobat.*

Hasil: *Pada analisis akhir, terdapat 150 pasien yang diikutsertakan dimana 88 pasien diantaranya lost to follow up. Setelah 5 hari terapi, rata-rata jumlah bab cair per hari telah turun dari 7,133±2,055 menjadi 0,733±0,8333 (p<0,0001). Efek samping yang terjadi berupa gastritis (5,33%), mual (10,66%), dan rasa metalik (3,33%).*

Simpulan*: Kombinasi dari rifaximin dan metronidazole secara signifikan menurunkan jumlah bab cair dan gejala penyerta serta bersifat efektif secara klinis dan aman sebagai terapi empirik untuk diare akut yang disebabkan oleh berbagai etiologi.*

Kata kunci: *diare akut, infeksi gastrointestinal campuran, rifaximin, metronidazole.*

INTRODUCTION

Diarrhea is defined as the passage of three or more loose or liquid stools per day (or more frequent passage than is normal for the individual).[1] Acute diarrhea is a commonly diagnosed condition among adults, causing significant morbidity worldwide. While it is often viewed as a major cause of childhood mortality in developing countries, adult mortality resulting from diarrhea is also common, especially during outbreaks. Poor sanitation and unhygienic eating habits contribute to the high prevalence of acute diarrhea among adults, with contaminated food and water being the primary culprits.[2] Diarrhea is most frequently caused by viruses, bacteria, and parasites, with fungi playing a minimal role, mainly in individuals with compromised immune systems. Common bacteria that cause diarrhea include *E. coli*, *Shigella* spp., *Salmonella* spp., and *Campylobacter* spp., while parasitic protozoa like *Giardia lamblia* and *Entamoeba histolytica* can lead to both temporary and chronic diarrhea. These parasites are known to spread widely because they are commonly found in food and water, and they exhibit resistance to to environmental factors and disinfection procedures.[3] The scientific community, over the past few decades, has established a consensus on the most effective measures to reduce the incidence, morbidity, and mortality of acute diarrhea. Some of the measures aimed at reducing the incidence of diarrheal diseases include clean water supply, adequate treatment of human waste, education, and food safety. Therapeutic management with emphasis on oral rehydration therapy and intravenous rehydration therapy, recommended since the 1970s, are milestones of twentieth-century medicine.[4] Since per capita income in India is low and most of gastrointestinal infections are mixed in nature, doctors prefer empirical therapy to ensure faster recovery without burdening the patient with additional investigations like stool culture .

Rifaximin is a semisynthetic derivative of rifamycin that acts by binding to the β-subunit of bacterial DNA-dependent RNA polymerase, resulting in inhibition of bacterial RNA synthesis. It has broad-spectrum activity against Gram-positive and Gram-negative aerobic and anaerobic bacteria. It shows activity against essentially all enteric bacterial pathogens, including *Clostridium difficle* and *Helicobacter pylori*. Being virtually unabsorbed, this antimicrobial has little value outside the area of enteric infections, thus minimizing both antimicrobial resistance and systemic adverse events. It has proved to be safe in all patient populations, including young children. Bacterial pathogens show a low potential for developing resistance during rifaximin therapy. When rifaximin resistance to gut flora did occur during therapy, the resistance was unstable. Rifaximin has surprisingly little effect on both Gram-positive and Gram-negative flora of the colon.[5]

Metronidazole is an antimicrobial agent that has been used in clinical medicine for more than 45 years. It has been shown to be effective against protozoal infections, such as amebiasis and giardiasis. It has high activity against Gram-negative anaerobic bacteria, such as *B. fragilis,* and Gram-positive anaerobic bacteria, such as *C. difficile.* Metronidazole with its good activity against pathogenic anaerobic bacteria, favorable pharmacokinetic and pharmacodynamic properties and minor adverse effects is considered to be a cost-effective drug.[6] In light of the above evidences, the current study proposes fixed-dose combination (FDC) of rifaximin and metronidazole as a useful

treatment option in the management of acute diarrhea and associated symptoms.

METHOD

Study Design and Patients

This study was an open-label, non-comparative, non-randomized, multicenter trial in 238 patients who visited panel doctors with acute diarrhea in 23 different clinics located in various parts of India. Patients (men and non-pregnant women) were eligible for this study if; they were suffering from acute diarrhea, aged > 18 years. We excluded patients with known/suspected history of hypersensitivity to any of the related drugs, colitis, gastrointestinal bleeding, known cases of renal or hepatic insufficiency, cardiac diseases, pregnant, or lactating women. Since this was an observational study and was conducted post-approval of the drug by the state Food and Drug Administration (FDA); informed consent and ethical approval were not mandatory.

Treatment and Duration of Treatment

Patients were given 1 tablet of Rifaxigyl-M® containing rifaximin 200 mg and metronidazole 400 mg twice daily for 5 days. Oral rehydrating solution was also prescribed according to the patient's dehydration status. No other additional drugs were prescribed during the study.

Assessment of Primary Outcome Measure

The number of soft or watery stools, body temperature, nausea, vomiting, abdominal pain, and gas/flatus are parameters that were evaluated at baseline, day 3, and day 5 of the study.

Assessment of Secondary Outcome Measure

Efficacy and tolerability were evaluated based on the global assessment by the investigator on a 3-point scale marked as excellent/good/poor. Adverse events were recorded and the action taken was documented.

Statistical Analysis

Statistical analysis was done by "paired t-test" for each parameter compared with change from baseline to day 5. The minimum level of significance was fixed at 95% confidence limit and $p < 0.05$ was considered significant. All the statistical analysis was performed by using Graph Pad Prism 9 version 9.5.1.

RESULTS

A total of 238 patients were recruited in the study. 150 patients were included in the final analysis and 88 patients were lost to follow-up. A large number of patients were lost to follow up because there is a possibility that they recovered from illness and did not feel the need to report. The recruited patients were in the age range of 18 to 84 years (mean age 42.58 ± 12.26).

Table 1. Baseline and post-treatment clinical characteristics

Clinical symptoms	Number (%)		
	Baseline	Day 3	Day 5
Fever	64 (42.66%)	4 (2.66%)	0 (0%)
Nausea	88 (58.66%)	16 (10.66%)	0 (0%)
Vomiting	80 (53.33%)	13 (8.66%)	0 (0%)
Abdominal pain	98 (65.33%)	15 (10%)	0 (0%)
Gas/flatus	56 (37.33%)	13 (8.66%)	0 (0%)

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 + metronidazole fixed-dose combination as compared to baseline. Number of stools per day reduced from 7.133 ± 2.055 to 0.733 ± 0.833 ($p < 0.0001$).

Other Parameters

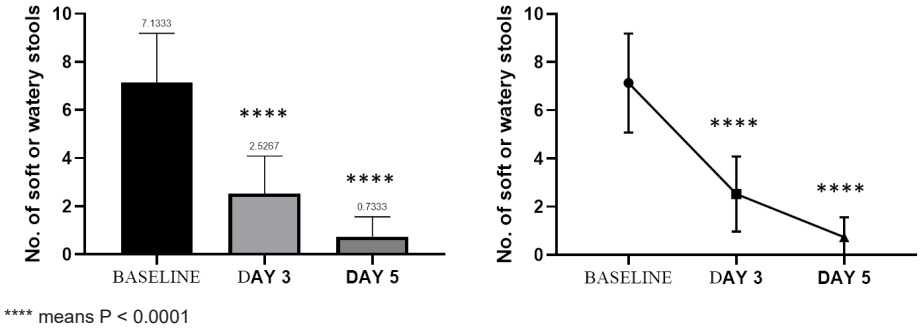
Out of 150 patients, 42.66% patients reported fever, 58.66% reported nausea, 53.33% reported vomiting, 65.33% reported abdominal pain, and 37.33% reported gas/flatus at baseline. All the patients reported no symptoms at the end of the trial.

Safety Evaluation

Incidences of gastritis, nausea, and metallic taste were reported in 5.33%, 10.66%, and 3.33% of patients respectively. None of the patients withdrew from the study due to adverse events.

Global Assessment of Efficacy and Tolerability

As per investigators' assessment of the efficacy of rifaximin + metronidazole fixed-dose combination, 63.33% of patients reported excellent, 36% of patients reported good, and 0.66% of patients reported poor efficacy. As per investigators' assessment of the tolerability, 67.33% of patients reported excellent, 32% of patients reported good, and 0.66% of patients reported poor tolerability.



**** means P < 0.0001

Figure 1. The mean reduction in number of watery stools

DISCUSSION

Diarrhea is the prevailing result of gastrointestinal tract infections, which typically have a multifaceted etiology. To effectively manage these mixed gastrointestinal infections, a combination therapy consisting of a broad-spectrum antibiotic and an antiprotozoal drug is a more rational approach. Cost is a concern even today and therefore doctors do not advise stool examination frequently and prefer empirical treatment with a combination covering bacteria and protozoa, as these are common ones because of unhygienic conditions prevailing in the country. This not only reduces the overall cost of therapy but also reduces the number of man days lost and consequently wages lost due to diarrhea.

Rifaximin has shown efficacy and tolerability in several clinical studies and systematic reviews which included patients with travelers' diarrhea, small intestinal bacterial overgrowth (SIBO), diarrhea-predominant irritable bowel syndrome, and hepatic encephalopathy.[7–10] Rifaximin has also shown therapeutic potential in the management of *Clostridium difficile* infection (CDI), especially in CDI recurrences.[11] A good evidence supporting the use of rifaximin as a chemoprophylactic agent in travelers' diarrhea, especially in individuals who are at high risk of severe complications from acute infectious diarrhea is available.[12] Because rifaximin is non-absorbed, there is an absence of systemic drug interactions and the drug possesses an excellent safety profile due to limited potential for side effects. Therefore, this gut-selective antibiotic appears to be a promising agent for the treatment of acute infectious diarrhea and in chemoprophylaxis for travelers' diarrhea.

It is found that in mixed gastrointestinal infections, 73% of patients were most often detected with protozoa including *Giardia lamblia*, *Entamoeba histolytica*, and *Cryptosporidium* spp.[13] As metronidazole is still successfully used due to its efficacy against protozoal infections for the treatment of trichomoniasis, amoebiasis, and giardiasis, it should complement rifaximin in treating mixed infections.[6]

In the present study, a combination of rifaximin and metronidazole significantly reduced the number of soft or watery stools. At the end of the study, all patients were afebrile. Symptoms associated with diarrhea such as nausea, vomiting, abdominal pain, and gas/flatus were significantly reduced after using rifaximin and metronidazole combination. None of the patients withdrew from the study due to adverse events. Minor incidences of gastritis, nausea and metallic taste were reported. Thus, based on available clinical studies and present clinical data, rifaximin in combination with metronidazole is a safe and effective option for the management of acute diarrhea due to mixed infections.

Limitation of the study: Although the combination is found to have a significantly favorable response, one of the major limitations of the study is that patients were not subjected to stool examination. The reason for not doing stool examination is that most of the time gastrointestinal infections is of mixed origin and subjecting the patients to get the stool examination is an additional cost to the patient in the prevailing low per capita income of the majority of the household. The study results would have been more unbiased if a routine stool examination was performed to rule out diarrhea due to exclusive viral origin; a self-limiting illness.

CONCLUSION

Acute diarrhea is a serious concern in India. In a quest for an effective and safer combination for acute diarrhea, FDC of rifaximin and metronidazole can be a new armamentarium in the management of acute diarrhea. A combination of rifaximin and metronidazole significantly reduced the frequency of diarrhea and other associated symptoms with excellent efficacy and tolerability. Therefore, FDC of rifaximin and metronidazole is an innovative safe and effective option for the management of acute diarrheal episodes.

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REFERENCES

1. Ministry of Health and Family Welfare Government of India. National Guidelines for Infection Prevention and Control in Healthcare Facilities [Internet]. India: National Centre for Disease Control, Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India; 2020 [cited 2023 Mar 08]. Available from: https://www.mohfw.gov.in/pdf/National%20Guidelines%20for%20IPC%20in%2 0HCF%20-%20final%281%29.pdf.
2. Manatsathit S, Dupont HL, Farthing M, Kositchaiwat C, Leelakusolvong S, Ramakrishna BS, et al. Guideline for the management of acute diarrhea in adults. J Gastroenterol Hepatol. 2002;17 Suppl:S54 –71.
3. DuPont HL. Community acquired diarrheal disease in western countries: application of nonabsorbable oral antibiotic therapy. Adv Stud Med. 2003;3:S945–50.
4. Brandt KG, Antunes MM, da Silva GA. Acute diarrhea: evidence-based management. J Pediatr (Rio J). 2015;91(6 Suppl 1):S36–43.
5. Huang DB, DuPont HL. Rifaximin--a novel antimicrobial for enteric infections. J Infect. 2005;50:97–106.
6. Löfmark S, Edlund C, Nord CE. Metronidazole is still the drug of choice for treatment of anaerobic infections. Clin Infect Dis. 2010;50 Suppl 1:S16–23.
7. Layer P, Andresen V. Review article: rifaximin, a minimally absorbed oral antibacterial, for the treatment of travellers' diarrhoea. Aliment Pharmacol Ther. 2010;31:1155–64.
8. 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;15:1385–99.
9. 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;11:335–45.
10. 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;31:434–50.
11. 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;55:35–9.
12. 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;24(5).
13. Lindsay B, Ramamurthy T, Gupta SS, Takeda Y, Rajendran K, Nair GB, et al. Diarrheagenic pathogens in polymicrobial infections. Emerg Infect Dis. 2011;17:606–11.