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EVALUATION OF EFFICACY AND TOLERABILITY OF FIXED DOSE COMBINATION OF RIFAXIMIN AND METRONIDAZOLE IN THE MANAGEMENT OF IRRITABLE BOWEL SYNDROME WITH DIARRHEA

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ABSTRACT:

Irritable bowel syndrome, a prevalent functional bowel disorder, significantly affects patients' everyday lives and imposes a substantial economic burden on society. However, treatments options for managing diarrhea-predominant irritable bowel syndrome are limited. Rifaximin along with metronidazole is proposed as a treatment option for irritable bowel syndrome with diarrhea. The aim of this study was to evaluate the efficacy and tolerability of a fixed dose combination of rifaximin and metronidazole in the management of irritable bowel syndrome with diarrhea. An open-label, non-comparative, non-randomized, multicentre trial was conducted in 25 subjects presenting with acute diarrheal episodes associated with irritable bowel syndrome. The study was approved by institutional research ethics committee and participants provided signed informed consent. Patients were given fixed dose combination tablet containing rifaximin 200mg and metronidazole 400mg twice daily for 5 days. Primary outcomes were change from baseline in number of soft or watery stools, abdominal pain and gas/flatulence at day 5. Efficacy and tolerability was evaluated based on the global assessment by the investigators on a 3 point scale marked as Excellent/Good/Poor. Adverse drug reaction was assessed throughout the study period. After 5 days of therapy, mean number of watery stool per day were reduced from 7.6 ± 2.958 to 0.96 ± 1.098 ($P<0.0001$). None of the patients reported abdominal pain or gas/flatulence at end of study. As per investigators assessment all patients reported good to excellent efficacy and tolerability. Minor incidences of gastritis, nausea and metallic taste were reported in 12%, 12% and 8% patients respectively. In conclusion, combination of rifaximin and metronidazole significantly reduces number of watery stools and associated symptoms and is a clinically effective and safe option in the management of acute diarrhea associated with irritable bowel syndrome.

Keywords: Acute diarrhea, irritable bowel syndrome, rifaximin, metronidazole

INTRODUCTION:

Irritable bowel syndrome (IBS) is a type of functional bowel disorder that is characterized by recurring abdominal pain and a change in bowel habits, often accompanied by abdominal bloating [1]. It affects about 20% of the general population, mainly women. The diagnosis of IBS is based on the Rome IV criteria, which requires the presence of recurrent abdominal pain at least once per week during the previous three months and associated with at least two of the following: defecation, alterations in stool frequency, and changes in stool form [2]. IBS is further classified into different types based on the predominant bowel habit, which includes constipation-predominant IBS, diarrhea-predominant IBS (IBS-D), or mixed-form IBS. IBS and IBS-D in particular are known to negatively impact a person's quality of life and increase healthcare costs [2].

Irritable bowel syndrome (IBS) is a complex disorder with a multifactorial etiology, involving alterations in gut microbiota, gastrointestinal motility, microscopic inflammation, bile acid malabsorption, and alterations in the enteric nervous system. There is no gold standard of treatment, and a personalized approach is necessary [1].

Management includes patient education, stress reduction, and dietary advice. In patients with IBS-D, therapeutic options include antibiotics, peripheral opioid agonists, mixed opioid agonists/antagonists, bile acid sequestrants and antagonists of serotonin 5-hydroxytryptamine type 3 receptors [2].

Loperamide may reduce the frequency of bowel movements and improve stool consistency, but it does not improve global IBS symptoms or abdominal pain and can cause constipation. A strong physician-patient relationship is essential in managing IBS. Eluxadoline is a mixed μ-opioid agonist and δ-opioid antagonist used to slow bowel motility and reduce visceral pain in IBS-D patients. However, it can cause constipation and nausea and is contraindicated in patients with a history of pancreatitis, bile duct obstruction, sphincter of Oddi dysfunction or alcohol abuse. Bile acid sequestrants, such as cholestyramine, colestipol, and colesevelam, can also be effective in improving stool consistency and decreasing bowel movements, particularly in patients with bile acid malabsorption, but can cause constipation and interfere with drug absorption.

Antagonists of serotonin 5-HT3 receptors, such as alosetron, ondansetron, and ramosetron, can be effective in reducing abdominal pain and improving stool frequency and consistency in selected patients with IBS-D, but can cause

constipation and ischemic colitis, and should be used with caution [2].

Rifaximin is a non-absorbable rifamycin that has been shown to be effective in reducing IBS symptoms, bloating, and loose or watery stools after 2 weeks of treatment, and is well-tolerated with no significant adverse events [3]. It has also been found to be safe and effective in repeated treatments of recurrent symptoms [4]. Moreover, rifaximin eradicates small intestinal bacterial overgrowth (SIBO) in patients with IBS, with results sustained up to 10 weeks post-treatment [5]. Metronidazole is an antimicrobial agent that has been used in clinical medicine for more than 45 years [6]. It has shown to provide symptom relief in irritable bowel syndrome, without affecting rectosigmoid motility [7] in addition to anti-protozoal and broad-spectrum anti-bacteria activity [6]. Metronidazole therapy also results in sustained improvement in pain, stool and total score in post-infectious irritable bowel syndrome (PIIBS) and diarrhoea-predominant IBS subgroups [8]. Considering the above evidence, the current study proposes fixed dose combination (FDC) of rifaximin and metronidazole as a useful treatment option in the management of acute diarrhea associated with irritable bowel syndrome.

METHODOLOGY:

Study design and patients

This study was an open-label, non-comparative, non-randomized, multicentre trial in 25 patients conducted in 10 clinics located at various parts of India. Patients (men and non-pregnant women having age >18 years) providing signed informed consent were eligible for this study based on following inclusion and exclusion criteria. The study was approved by the institutional research ethics committee.

Inclusion criteria

Patients fits Rome IV criteria for IBS with diarrhea (IBS-D), which is defined by >25% of abnormal bowel movements with Bristol stool form types 6 or 7 (loose, watery stool) and <25% of abnormal bowel movements with Bristol stool form types 1 or 2 (hard, lumpy stool).

Patients suffering from abdominal pain, on average, ≥1 day per week in previous 3 months, associated with ≥2 of the following: (1) Related to defecation, (2) Associated with a change in stool frequency, or (3) Associated with a change in form (appearance) of stool.

Colonoscopy must have been completed within the past 10 years.

Exclusion criteria

Patients with known/suspected history of hypersensitivity to any of the trial related drug, dysentery, colitis, gastrointestinal bleeding.

Taking rifaximin or any other antibiotic within past 60 days.

Known cases of renal or hepatic insufficiency, cardiac diseases or diabetes.

Pregnant or lactating women.

History of GI surgery.

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.

Assessment of Primary Outcome Measure

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

Number of soft or watery stools

Abdominal pain and

Gas/flatulence

Assessment of Secondary Outcome Measure

Efficacy and tolerability were evaluated based on the global assessment by the Investigators on a 3-point scale marked as Excellent/Good/Poor. Adverse event was recorded on a scale of scores 1 to 3 (1=mild, 2=moderate, 3=severe) 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 as significant. All the statistical analysis was performed by using Graph Pad Prism 9 version 9.5.1.

RESULTS:

A total of 25 patients were included for final analysis. The recruited patients were in the age range of 18 to 71 years (mean age 45.88 ± 10.84).

Number of soft or watery stools:

Number of stools per day was recorded at the start and end of the trial.

Statistically significant reduction in number of bowel movement was reported with rifaximin + metronidazole fixed dose combination as compared to baseline. Number of stools per day reduced from 7.6 ± 2.958 to 0.96 ± 1.098 (P<0.0001). The results are presented in Table 1 and illustrated in Figure 1

Table 1: Baseline and Post-treatment Clinical Characteristics

Clinical symptoms	Number (%)		
	Baseline	Day 3	Day 5
Number of soft or watery stools	7.6 ± 2.958	2.56 ± 1.685	0.96 ± 1.098
Abdominal Pain	22 (88%)	3 (12%)	0 (0%)
Gas/Flatulence	12 (48%)	2 (8%)	0 (0%)

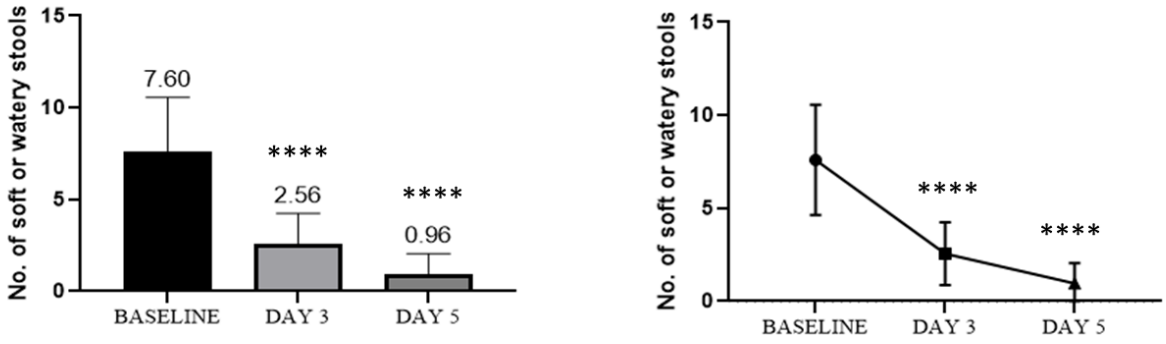

Figure 1: Mean reduction in number of watery stools. ****P<0.0001

Other Parameters

Out of 25 patients, 88% reported abdominal pain and 48% reported gas/flatulence 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 12%, 12%, and 8% of patients respectively. No serious adverse events were reported which led to withdrawal of patient from study.

Global assessment of efficacy and tolerability

As per investigators assessment about efficacy of rifaximin + metronidazole fixed dose combination, 72% patients reported excellent, 28% patients reported good and none of the patients reported poor efficacy. As per investigators assessment about tolerability, 60% patients reported excellent, 40% patients reported good and none of the patients reported poor tolerability.

DISCUSSION:

IBS-D is a chronic condition characterized by a complex interplay between the gut and brain without an identifiable structural pathology. The condition is heterogeneous and has a multifactorial, evolving pathophysiology involving alterations in visceral sensitivity, gut microbial changes, increased intestinal permeability, disrupted motility, and immune and neural-hormonal system involvement. GI-related infections may predispose individuals to post infectious IBS, which occurs after resolution of a GI-related infection and meets the diagnostic criteria for IBS, even without a prior history of IBS symptoms [9].

Rifaximin is a non-systemic antibiotic used to treat IBS-D, administered as short-course therapy. It has been shown to significantly improve global IBS symptoms, including bloating and loose or watery stools with good tolerability and a favorable safety profile [9]. In

two randomized, double-blind, clinical studies of patients with non-constipation IBS (n = 1260), a pooled analysis revealed a significantly larger percentage of patients treated with rifaximin to achieve adequate relief of global IBS symptoms versus placebo for at least two of the first 4 weeks post-treatment (40.7% vs 31.7%, respectively; P < 0.001) [5]. In a repeat treatment trial, 44.1% of 2579 patients were open-label responders to rifaximin (patients with at least a 50% reduction in frequency of loose stools for at least two of the first 4 weeks post-treatment plus at least a 30% decrease from baseline in abdominal pain). Initial responders with symptom recurrence entered a randomized, double-blind, placebo-controlled repeat treatment phase where a significantly higher percentage of responders were observed with rifaximin (n = 328) versus placebo (n = 308) for 2 weeks (38.1% vs 31.5%, respectively; P = 0.03) [4]. According to the ACG guideline for managing IBS, rifaximin is recommended as a treatment for global IBS-D symptoms [10]. Rifaximin was also found to be effective and safe in eradicating SIBO, in a systematic review and meta-analysis that analyzed a total of 21 observational studies and 5 RCTs involving 874 patients [11]. Because rifaximin is non-absorbed, there is an absence of systemic drug–drug interactions and the drug possess 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 diarrhea associated with IBS-D [5].

Metronidazole is frequently used in community practice in India to treat episodes of diarrhoea in patients with IBS and as an anti-protozoal and broad spectrum anti-bacterial. Most patients report relief of symptoms in the short-term treatment with this drug. Post-infectious irritable bowel syndrome accounts for 6%-17% of patients with IBS. Metronidazole therapy results in sustained improvement in pain, stool and total score in PIIBS and diarrhoea-predominant IBS subgroups [6, 7]. As metronidazole is an effective and safe treatment option for IBS-D it should complement rifaximin not only for a greater associated symptoms relief but also for post-infectious irritable bowel syndrome.

In the present study, combination of rifaximin and metronidazole in patients with IBS-D significantly reduced number of soft or watery stools. Symptoms associated such as abdominal pain and gas/flatulence were also significantly reduced. None of the patient withdrew from the study due to adverse events. Minor incidence 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 in patients with IBS-D.

CONCLUSION:

Acute diarrhea associated with IBS-D is a serious concern in India. In a quest for effective

and safer combination, FDC of rifaximin and metronidazole can be a new armamentarium in the management of IBS-D symptoms. Combination of rifaximin and metronidazole significantly reduced 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 associated with IBS-D.

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REFERENCES

1. Lacy BE. Review article: an analysis of safety profiles of treatments for diarrhoea-predominant irritable bowel syndrome. Aliment Pharmacol Ther. 2018 Oct;48(8):817-830.
2. Bonetto S, Fagoonee S, Battaglia E, Grassini M, Saracco GM, Pellicano R. Recent advances in the treatment of irritable bowel syndrome. Pol Arch Intern Med. 2021 August 30;131(7-8):709-715.
3. Pimentel M, Lembo A, Chey WD, Zakko S, Ringel Y, Yu J, Mareya SM, Shaw AL, Bortey E, Forbes WP; TARGET Study Group. Rifaximin therapy for patients with irritable bowel syndrome without constipation. N Engl J Med. 2011 Jan 6;364(1):22-32.
4. Lembo A, Pimentel M, Rao SS, Schoenfeld P, Cash B, Weinstock LB, Paterson C, Bortey E, Forbes WP. Repeat Treatment With Rifaximin Is Safe and Effective in Patients With Diarrhea-Predominant Irritable Bowel Syndrome. Gastroenterology. 2016 December; 151(6): 1113 - 1121.
5. Pimentel M. Review of rifaximin as treatment for SIBO and IBS. Expert Opin Investig Drugs. 2009 Mar;18(3):349-58.
6. 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.
7. Nayak AK, Karnad DR, Abraham P, Mistry FP. Metronidazole relieves symptoms in irritable bowel syndrome: the confusion with so-called 'chronic amebiasis'. Indian J Gastroenterol. 1997 Oct;16(4):137-9.
8. Thakur T, Altekar SB, Bapat MR, Rathi PM, Joshi A, Abraham P. Post-infectious irritable bowel syndrome: Role of metronidazole. Ann Gastroenterol. 2009;22(2):102–5.
9. Moshiree B, Heidelbaugh JJ, Sayuk GS. A Narrative Review of Irritable Bowel Syndrome with Diarrhea: A Primer for Primary Care Providers. Adv Ther. 2022 Sep;39(9):4003-4020.
10. Lacy BE, Pimentel M, Brenner DM, Chey WD, Keefer LA, Long MD, Moshiree B. ACG Clinical Guideline: Management of Irritable Bowel Syndrome. Am J Gastroenterol. 2021 Jan 1;116(1):17-44.
11. 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.