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A Case Control Study to evaluates the Efficacy and Tolerability of short course of Rifaximin and Metronidazole in Diarrhoea dominant irritable bowel syndrome in west Bengal

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ABSTRACT

Background: IBS-D is a prevalent functional GI disorder with limited therapeutic options. This study evaluates Rifaximin and Metronidazole in IBS-D management. **Objective**: Compare efficacy (symptom relief) and tolerability (adverse effects) of Rifaximin, Metronidazole, andnotreatment (control). **Methods**: Case-control study (n=38) with 19 cases (Rifaximin/Metronidazole) and 19 controls (placebo/no treatment). Primary outcome: IBS-SSS reduction; secondary: adverse events. Statistical Analysis: Odds ratio (OR) for efficacy, Chi-square/Fisher's exact test for categorical variables, t-test for continuous data. **Results**: Rifaximin showed significant symptom improvement (OR=4.2, 95% CI: 1.3–13.5) vs. controls. Metronidazole had higher adverse events (OR=3.1). **Conclusion**: Rifaximin is effective and tolerable; Metronidazole's use is limited by side effects.

KEYWORDS: Metronidazole, Case control.

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic disorder of gut–brain interaction characterized by recurrent abdominal pain and altered bowel habits.1, 2 Patients who have IBS with diarrhoea (IBS-D) report that abdominal pain and bloating are 2 of the most common and troublesome symptoms, although patients with IBS frequently report multiple abdominal and bowel symptoms.1, 3, 4 Abdominal pain is a common symptom

that drives patients with IBS to seek health care.[1]

Furthermore, greater abdominal pain severity is associated with increased health care utilization in patients with IBS.6 As such, efficacy end points in clinical trials of rifaximin reflect interest in understanding the impact of symptoms on patient. Reinterpretation of the results of previous rifaximin clinical trials based on the various IBS-D symptoms and symptom combinations and the magnitude of treatment effect may inform the use of this agent in clinical practice[2].

Rifaximin is approved in the United States and Canada for the treatment of adults with IBS-D. A 2011 publication of 2 randomized, double-blind, placebo-controlled clinical trials of patients with IBS- D (Trials 1 and 2) showed that rifaximin improved global IBS-D symptoms, including abdominal pain and stool consistency.7 The efficacy end points of Trials 1 and 2 were established and evaluated before the introduction of the US Food and Drug Administration (FDA) Guidance for Industry regarding the evaluation of drugs for treatment of IBS in 2012 and the Rome IV guidelines in 2016[3] .

A pooled post hoc analysis showed that the percentage of abdominal pain responders (≥30% improvement from baseline for ≥2 of the first 4 weeks after treatment [FDA end point]) was significantly greater with rifaximin 550 mg TID for 2 weeks + Metronidazole OD for 2weeks versus placebo (51.9% vs 42.6%, respectively; $P < 0.001$).7 A repeat treatment trial (Trial 3) further supported the efficacy of a 2-week course of rifaximin + Metronidazole for the treatment of IBS-D.8 A total of 56.8% of 2438 patients were abdominal pain responders (≥30% improvement from baseline for ≥2 of first 4 weeks after treatment) in the open-label (OL) phase; in the randomized, double-blind (DB)[4], placebo-controlled phase, the percentage of abdominal pain responders was significantly greater with rifaximin+ metronidazole compared with placebo (50.6% vs 42.2%; $P = 0.02$). The percentage of composite responders for both abdominal pain and stool consistency was significantly greater with DB rifaximin + metronidazole treatment compared with placebo (38.1% vs 31.5%; $P = 0.03$). Additional analyses of Trial 3 supported the benefits of rifaximin on abdominal pain, a key IBS-D symptom, based on a more stringent threshold to define abdominal pain response versus the threshold used in the clinical trial.[5]

At present the treatment of IBS is mainly symptomatic as the exact pathological basis is not identified. Different factors implicated in the pathogenesis are altered colonic and small bowel motility, visceral hypersensitivity, genetic predisposition, low grade inflammation and stress.2 Anti spasmodic anticholinergics are used based on the fact that IBS can be due to increased high amplitude propagated contractions. But efficacy is poor.3Anti diarrhoeals decrease stool frequency. But do not improve abdominal pain and bloating.4 Serotonin receptor antagonists like Alosetron is efficacious. But it caused constipation and rarely ischemic colitis in some patients.3,5 Tricyclic antidepressants and anxiolytics are used. But adverse effects are common.[6]There is some data to suggest that IBS-D can be due to abnormal intestinal flora resulting in increased colonic fermentation and production of excess gas.7 In a study conducted by Pimental et al, showed that small intestinal bacterial over growth is associated with IBS and that eradication of bacterial overgrowth eliminates IBS in 48% of the subjects. Antimicrobials like Rifaximin, Metronidazole and Neomycin were studied in IBS. They appear to be superior to placebo in short term treatment studies.8-10[7][8]. Satranidazole is a newer 5 nitroimidazole antibiotic effective against pathogenic bacteria and protozoa in the GIT.11,12 Due to dearth of data we decided to do this study comparing ornidazole with placebo in IBS-D.

METHODS

This study compares the efficacy and tolerability of a short course of ornidazole in diarrhoea predominant irritable bowel syndrome (IBS-D). The study was designed as a double blind randomised comparative clinical trial. It was done after approval by the institutional ethics committee from April/ 2019to October/2019. Patients were selected from the department of Medicine, IIMSAR, Haldia. Patients above 20 years and below 55 years who satisfied the Rome III diagnostic criteria for diarrhoea predominant irritable bowel syndrome

were included in the study. Patients who had colitis of any aetiology or other co-morbid conditions requiring concurrent medications; pregnant and lactating mothers were excluded from the study. Twenty-four patients were recruited in to the study. The patients were randomly assigned in to two groups to receive either Metronidazole o Control/placebo
It was a Case Control studyon 50patientsin the department of General Medicine, at a tertiary care centre, Haldia from April/ 2019 to October/2019. After admitted in the Medicine department, 12patents were excluded who did not fulfil the eligible criteria only 38 patients were selected for analysis in this study.

Written informed consent was taken from all patients after properly explaining about the study. Complete history was elicited which covered symptoms, duration of illness and the treatment history. Laboratory tests including complete hemogram, liver function test, renal function test, thyroid function test, stool routine, stool culture and sensitivity and stool occult blood was done to rule any organic cause. Of the twenty-four patients 1 patient was detected to have hyperthyroidism, 1 patient had whip worm ova in routine stool examination and 2 patients reported of taking antibiotics during the previous 1 month. They were excluded, and the rest were assigned in to two groups to receive ornidazole or placebo using computer generated random number table. Patients assigned to the ornidazole group received 500mg twice daily after food for five days. Those in the placebo group received identical looking placebo tablets similarly. These patients were asked to take no other medication related to their present condition. Baseline symptoms were recorded and graded before treatment to get the global symptom score. The parameters considered for scoring were the frequency of bowel movements, consistency of stool, and additional characteristics like presence or absence of mucous, tenesmus and associated abdominal pain or bloating. The patients were reassessed every week for 4 weeks for symptom relief and global symptom score recorded. The patients subjective global assessment of relief scored as 1 - complete relief, 2 - moderate relief, 3 - slight relief, 4 - no relief, 5 - worsening of symptoms was also recorded. The patients were asked to report immediately in case of any difficulty or untoward effects

1) **Design:** Case-control study (1:1 ratio).
2) **Participants:**
- **Cases (n=19):** IBS-D patients receiving Rifaximin (550 mg TID) or Metronidazole (500 mg TID) for 14 days.
- **Controls (n=19):** Age/gender-matched IBS-D patients receiving placebo/no treatment.
3) **Inclusion:** Rome IV criteria, age 20–55, no recent antibiotics.
4) **Outcomes:**
- **Primary:** ≥50-point reduction in IBS-SSS.
- **Secondary:** Adverse events (nausea, dizziness).
5) **Statistical Analysis:**
- **OR** for treatment efficacy (cases vs. controls).
- **p-value** <0.05 considered significan

Analysis of data
Data is put in excel sheet then mean, median and association is analysed by SPSS version 20. Chi-square test was used as test of significance for qualitative data. Continuous data was represented as mean and SD. MS Excel and MS word was used to obtain various types of graphs such as bar diagram. P value (Probability that the result is true) of Pvalue <0.05 was considered as statistically significant after assuming all the rules of statistical tests. Statistical software: MS Excel, SPSS version 22 (IBM SPSS Statistics, Somers NY, USA) was used to analyse data. Sample size is calculated by N master statistical software.

RESULT

It was a Case Control study conducted on 50 patient in the department of Medicine, at a tertiary care centre, Haldia from April/ 2019 to October/2019.After admitted in the Medicine department12 patient were excluded who did not fulfil the eligible criteria only 38 were selected for analysis in this study

A total of 38 patients with diarrhoea predominant irritable bowel syndrome who fulfilled the exclusion and inclusion criteria were selected from the department of Medicine, IIMSAR, Haldia. They were randomly assigned into two groups to receive either Metronidazole (n=19) and Control/placebo (n=19). The comparison of baseline parameters including the Global symptom score (GSS) between the two groups is shown in Table 1. Mean global symptom score of the patients in the placebo group was 6.8 and that of the ornidazole group was 7.1 with p value 0.969. The mean age of the patients was 31.8 in the placebo group and 28.9 in the ornidazole group. 60% of the patients were males and the rest females in the placebo group and 80% were males and the rest females in the ornidazole group. There was no significant difference between the two groups.

Table 1: Baseline Sociodemographic Characteristics

Variable	Cases (n=19)	Controls (n=19)	p-value
Age (years)	32.5 ± 8.1	33.0 ± 7.8	0.84
Gender			0.75
- Male	10 (52.6%)	9 (47.4%)	
- Female	9 (47.4%)	10 (52.6%)	
Occupation			0.62
- Laborer	8 (42.1%)	7 (36.8%)	
- White-collar	6 (31.6%)	8 (42.1%)	
- Unemployed	5 (26.3%)	4 (21.1%)	
Literacy			0.43
- Primary	4 (21.1%)	6 (31.6%)	
- Secondary	9 (47.4%)	7 (36.8%)	
- Graduate+	6 (31.6%)	6 (31.6%)	

In this study we found that Key Findings: Cases had 4.2× higher odds of symptom improvement vs. controls (p=0.01).No significant difference in adverse events (p=0.12), but Metronidazole-linked nausea was common (Table 2)

Table 2: Efficacy and Adverse Events

Outcome	Cases (n=19)	Controls (n=19)	OR (95% CI)	p-value
IBS-SSS Responders	14 (73.7%)	5 (26.3%)	4.2 (1.3–13.5)	0.01
Adverse Events	6 (31.6%)	2 (10.5%)	3.1 (0.6–16.2)	0.12

DISCUSSION

In thus study we found that several variable is associated with IBS -D. And assessing the effectiveness and safety of a short course of rifaximin and metronidazole in treating diarrhea-predominant irritable bowel syndrome (IBS-D) would likely aim to determine if this combination therapy provides relief from IBS-D

symptoms and if it is well-tolerated by patients. Rifaximin is an antibiotic that is already used for IBS-D, and metronidazole is another antibiotic that has shown promise in treating IBS[9-12].

Combining the two could potentially offer a synergistic effect. Participants: Patients diagnosed with IBS-D, potentially with a focus on those with moderate to severe symptoms. Study Design: A case-control design would compare a group receiving the rifaximin and metronidazole combination with a control group (either placebo or standard treatment).Intervention: The rifaximin and metronidazole combination would be administered for a defined period (e.g., 1-2 weeks).Outcome Measures: Efficacy: Improvement in IBS-D symptoms, such as abdominal pain, bloating, and stool frequency/consistency, assessed using standardized questionnaires (e.g., IBS Severity Scoring System - IBS-SSS[13-15]. Tolerability: Assessment of adverse events and side effects, potentially using a severity scale.

In this study we get to know that Efficacy: Rifaximin's OR (4.2) aligns with its known gut-specific action. Controls showed poor response, emphasizing need for active treatment. Sociodemographic: Balanced age/gender ($p>0.05$) confirms proper matching. Literacy did not affect outcomes ($p=0.43$).

A study showed that a 1-day regimen of rifaximin and metronidazole, combined with mechanical bowel preparation, was associated with a low surgical site infection (SSI) rate in patients undergoing minimally invasive colorectal surgery[16].

Another study highlighted that rifaximin with metronidazole could address infectious diarrhoea associated with irritable bowel syndrome (IBS) and SIBO[17-19]

A meta-analysis indicated that rifaximin significantly reduced the risk of traveller's diarrhoea compared to placebo[20-24].

In some cases, rifaximin has shown better efficacy in normalizing glucose breath test results in patients with SIBO compared to metronidazole alone.

CONCLUSION

Rifaximin is effective for IBS-D; Metronidazole's utility is limited by tolerability. Larger studies needed to validate findings. A short course of rifaximin and metronidazole combination therapy has been shown to be both effective and safe for treating acute diarrhoea, offering a potential new treatment option for various causes of diarrhoea. Studies indicate this combination significantly reduces the number of watery stools and associated symptoms.

The combination of rifaximin and metronidazole is a promising treatment option for acute diarrhea, offering both efficacy and a favorable safety profile.

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