Original Article

Efficacy of Rifaximin in Ulcerative Colitis Patient with Mild to Moderate Flare Up: A Randomized Controlled Trial

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Abstract

Background: Gut microbiota is now being considered an important factor in promoting and maintaining inflammation in inflammatory bowel disease as well as in ulcerative colitis. Enteric infection is a common cause of microbial dysbiosis and is frequently found in ulcerative colitis patients. Traditional antibiotics use may induce untoward effect during long term use. Rifaximin, a rifampicin derivative is virtually unabsorbed after oral administration and does not cause serious systemic side effects. The potential therapeutic activity of Rifaximin in ulcerative colitis patients during mild to moderate flare up is not determined clearly still now.

Objectives: To assess efficacy of Rifaximin in ulcerative colitis patients with mild to moderate flare up.

Materials & Methods: This open label randomized controlled trial was conducted among 100 ulcerative colitis patients with mild to moderate disease. Intervention group received Rifaximin 550 mg twice daily along with 2.4 gm/d Mesalamine for 28 days. Control group received maximum dose of mesalamine 4.8 gm/ day for 28 days. All the patients were assessed by Partial Mayo Score along with CBC with ESR, CRP, Stool R/E, C/S, S. Albumin, Fecal Calprotectin at baseline and after 28 days.

Results: In patients with mild disease activity 56.9% of patients were in Rifaximin group and 43.1% were in Mesalamine group. In patients with moderate disease activity 53.1% were in Rifaximin with Mesalamine group and 46.1% were in Masalamine group. After 28 days of intervention in Rifaximin with Mesalamine group 54.5% patients achieve remission with a statistically significant difference over Mesalamine group (33.1%), 43.6% patients had mild disease activity, 1.8% patients had moderate disease activity, none of the patients had severe disease whether 20% patient from Mesalamine group developed severe disease after intervention. Side effects including hair fall and constipation were more in control group.

Conclusion: Patient response to Rifaximin in ulcerative colitis with mild to moderate flare up appears to be favorable in this randomized controlled trial. To establish its efficacy longer follow up is warranted.

Keywords: Gut microbiota, Ulcerative colitis, Partial Mayo Score, Rifaximin.

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Introduction:

Inflammatory bowel disease (IBD) is characterized by repetitive episodes of inflammation of GIT caused by an abnormal immune response to gut microflora in a susceptible individual. Ulcerative colitis (UC) affects the rectum mostly, but it may involve whole colon up to caecum usually in a continuous fashion. Crohn's disease (CD) result in trans mural ulceration of any portion of GIT most often affecting the ileo-colonic region.[1]

Although most IBD occurs in people aged 15 to 30 years, up to 25% of patients will develop IBD by adolescence. There may be a bimodal distribution with a 2nd peak of 10% to 15% developing IBD after age 60 years.[2]

The etiology of IBD still remains obscure. Genetic, immunological, environmental and psychological factors all play a role in the pathophysiology of IBD. This immunological activity causes release of inflammatory mediators which not only serve to amplify the immune and inflammatory response, but they also have direct effects on epithelial function and on repair mechanisms, thus increasing collagen synthesis.[3] A breakdown in the qualitative balance between protective and harmful bacteria proposed as potential mechanism.[4] Microbial dysbiosis in ulcerative colitis patients may result in increase in inflammatory cytokine levels and mucosal permeability may contribute to more intestinal wall damage.[5] In IBD patient luminal bacteria shows decrease in beneficial bacteria and increase in pathogenic bacteria.[6]

Various meta-analysis has demonstrated that antibiotics such as metronidazole, ciprofloxacin, clofazimine and antibiotic combination can be successfully employed in IBD including Ulcerative Colitis.[7]

Rifaximin, α-polymer, a rifampicin derivative, is a locally acting antibacterial agent that is unabsorbed after oral administration, is mostly exerted as unchanged drug in the stools in the course of intestinal disorders, and thus devoid of systemic side effect.

5-Aminosalicylic acid derivatives have a variety of anti-inflammatory effects, considered as mainstay of treatment during mild to moderate flare up and during remission .5 - ASA derivatives reduce fecal concentration of sulfide. Therefore, some bacteria harbor in intestinal mucosa and damage the protective structure. Antibiotics may result in positive outcomes by destroying the pathogenic bacteria.

Materials & Methods

This randomized controlled clinical trial was conducted among patients of both sexes aged more than 18 years attending IBD clinic, inpatient and outpatient of Gastroenterology department, BSMMU in between January 2022 to June 2023, who (n=100) met the selection criteria including

mild to moderate flare up of ulcerative colitis using Truelove and Witts criteria initially enrolled for the study.

All of them were previously diagnosed as Ulcerative Colitis by compatible history, examination, biochemical, endoscopic and histological findings. Sampling was done by convenient and judgmental sampling. Study population was allocated into two groups: Mesalamine (n=45) and Rifaximin group with Mesalamine group (n=55) by randomization. Randomization was done by lottery. All the patients of both groups were assessed by their clinical history, examination and some biochemical parameters eg: CBC with ESR, CRP, Stool R/E, C/S, S. albumin, Fecal calprotectin. They were assessed by Partial Mayo Scoring Index of ulcerative colitis at baseline. All of them were maintained with Mesalamine 2.4gm/day. There was no blinding in drug distribution. After giving consent Mesalamine group received maximum dose of Mesalamine up to 4.8 g/day for four weeks for induction of remission. Rifaximin with Mesalamine group received Rifaximin 550mg twice daily for 4 weeks in addition to maintenance dose of Mesalamine (2.4 gm/day) for induction. Throughout the study they were advised to continue their usual dietary practice. Within these four weeks they did not receive any other medication. Adverse drug reactions were documented. No serious adverse event was not noticed during study period. After four weeks they were assessed by Partial Mayo Scoring Index of ulcerative colitis. Some biochemical tests were done at the end of the therapy eg: CBC with ESR, CRP, S. Albumin and data were recorded in data collection sheet. If the condition deteriorated then he was excluded from the study.

Result

Among study population mean age of Rifaximin with Mesalamine group was 32.78 years and mean age of Mesalamine group was 35.96 years. Left sided colitis was more prevalent both in Rifaximin with Mesalamine group (49.1%) & Mesalamine group (50.9%). In Rifaximin with Mesalamine group pouchitis was present in four patients but no one in Mesalamine group. At the time of enrollment, disease severity was assessed by Truelove and Witts criteria of ulcerative colitis. In intervention group 56.9% had mild disease and 53.1% had moderate disease activity. Disease severity assessed by Partial Mayo Scoring index of ulcerative colitis (mild and moderate) at baseline showed no statistically significant difference between two groups. Hb%, CRP, S. albumin & Fecal calprotectin at baseline between two groups showed no statistical difference (Table I). But after 28 days of treatment significant improvement was noticed in intervention group.

Table I: Disease severity of UC patients at baseline

Variables	Intervention group Rifaximin with Mesalamine group (55)	Control group Mesalamine group (45)	P value
Partial Mayo score (after 28 days)			
Remission	30 (54.5%)	15 (33.3%)	**0.001^{S}**
Mild	24 (43.6%)	12 (26.7%)	
Moderate	1 (1.8%)	9 (20%)	
Severe	0 (0%)	9 (20%)	

When subgroups of Partial Mayo Scoring index of UC between two groups were observed it showed that patient's improvement was more marked in Rifaximin group in terms of stool frequency. In Rifaximin with Mesalamine group no patient developed stool frequency more than five times than normal whereas 13.3% patients developed stool frequency more than 5 times than normal in Mesalamine group. After 28 days of intervention only serum albumin exhibits statistically significant P value between two groups (Table II).

Table II: Distribution of the participants according to components of Partial Mayo scoring index of UC after intervention.

Variables	Intervention group Rifaximin with Mesalamine group (55)	Control group Mesalamine group (45)
1-2 stools more than normal	37 (67.3%)	3 (6.7%)
3-4 stools more than normal	18 (32.7%)	36 (80%)
5 or more stools more than normal	0	6 (13.3%)
Rectal Bleeding		
No blood seen	11 (20%)	2 (4.4%)
Streaks of blood	23 (41.8%)	9 (20%)
Obvious blood with stool	20 (36.4%)	30 (66.7%)
Blood alone	1 (1.8%)	
Physicians global assessment		
Normal	11 (20%)	1 (2.2%)
Mild disease	25 (45.5%)	21 (46.7%)
Moderate disease	19 (34.5%)	18 (40%)
Severe disease	0	5 (11.1%)

Among adverse drug reaction, constipation and hair fall were reported in both groups. Patient who developed hair fall during invervention, among them 75% belong to Mesalamine group whereas 25% were in Rifaximin with Mesalamine group. Constipation was also more prevalent in Mesalamine group.

Discussion

Given the chronicity of the disease, it is always important to explore effective therapeutic options with less side effects. Recent guidelines recommend using maximum dose of Mesalamine in mild to moderate ulcerative colitis. Though safety profile of Mesalamine is high, sometimes it carries serious dose dependent side effects eg: pancreatitis, bone marrow suppression, impaired liver function, interstitial nephritis.[8] So if we can use gut friendly antibiotic targeting intestinal dysbiosis in mild to moderate ulcerative colitis, it may create a new treatment strategy for ulcerative colitis patients.

In this trial, it was found that major portion of participants (40%) fell in the 26-35 age group, with an average age of 34.21 years. Regarding gender distribution, most of the participants were male (65%). Chowdhury et al. (2013) conducted a study in BSMMU, Dhaka showed similar demographic profile with mean age 34.14 years.[9] It was also a male predominant study. A study conducted by Lamet in 2011 had similar demographic characteristics as this study; with exception that it was a female predominant study.[10]

Regarding involvement of ulcerative colitis, in the Rifaximin with Mesalamine group, more patients were diagnosed as left sided colitis previously. Then pancolitis followed by proctitis and pouchitis were more prevalent. In Mesalamine group left sided colitis was more observed than proctitis and pancolitis. Previous study showed that proctitis and proctosigmoiditis were more prevalent and pancolitis was least prevalent in mesalamine group.[11] Variation may be related to geographical and environmental differences of study place. Further larger study is needed to explore the extent of involvement in ulcerative colitis in our country.

At baseline all the patients were assessed by Partial Mayo Scoring Index of Ulcerative Colitis. After 28 days of intervention two groups were assessed again with Partial Mayo Scoring index of ulcerative colitis. A significant (P<0.001) association was found in the Partial Mayo Score after 28 days of intervention, where Rifaximin with Mesalamine had more remission (54.5%) than Mesalamine (33.3%) group.

Antibiotics are not standard therapy, and their effects are still under investigation and a matter of debate. Previous studies showed a correlation between changes in the composition of the intestinal microbiota and IBD. At the moment current guidelines do not recommend use of antibiotics in IBD, except for the treatment of septic complication of crohns disease and pouchitis. A meta-analysis from 2012 included 11 randomized controlled trials, involving 832 crohns disease patient, treated with broad spectrum antibiotics, including Ciprofloxacin, Metronidazole, Combination, Rifaximin and others.[12] Treatment duration was variable between 2-16 weeks. Clinical improvement occurred in antibiotic group (56.1%) compared to placebo group (37.9%). Yuriko Nishikawa (2021) reported that combination of Amoxicillin, Fosfomycin and Metronidazole compared with Amoxicillin, Tetracycline and Metronidazole was more effective and safer in active ulcerative colitis .[13] Long term use of systemic antibiotics such as Metronidazole and Ciprofloxacin is associated with high number of adverse effects. Rifaximin is a rifamycin derived antibiotic that has a large antimicrobial coverage against Gram positive and Gram-negative bacteria including aerobes and anaerobes and poor absorption after oral administration and complete fecal excretion as unchanged drug. An open label pilot study conducted by Guslandi in 2004 showed statistically significant response with Rifaximin in ulcerative colitis flare patients.[14] But the study conducted by Goinchetti in 1999 showed no statistically significant difference between Rifaximin and placebo group in steroid refractory severe ulcerative colitis patients in their clinical outcome.[15] But there was more reduction of stool frequency in Rifaximin group over the placebo group. Variation of result may be due to disease severity as they conducted their study upon severe ulcerative colitis patients.

Rifaximin is a gut specific human pregnane X receptor (PXR) agonist.[16] PXR is a ligand activated transcription factor important drug transcription and metabolism. Recent data suggests PXR may play role in pathogenesis of IBD. Langmann et al. (2004) showed that gene expression analysis of tissue obtained from ulcerative colitis patients a significant reduction of PXR activity compared to normal intestinal tissue.[17]

Cheng et al. (2010) showed that preventive and therapeutic role of Rifaximin on IBD through human PXR mediated inhibition of NF-KB signaling cascade, suggesting that human PXR may be an effective target in treatment of IBD.[18]

In mild relapse of ulcerative colitis, aggressive treatment with immunosuppressive (Corticosteroid, azathioprine, biologic therapy) may be associated with higher rate of possible side effect.[19] In this study mean of Partial Mayo Score between two groups after intervention showed statistically significant difference; more reduction of score was observed in Rifaximin group. So, if Rifaximin is added with maintenance dose of Mesalamine may be a new approach in mild to moderate ulcerative colitis patients who have history of intolerance to high dose Mesalamine and may open a corticosteroid sparing regimen as patient intolerant to high dose Mesalamine are usually treated with corticosteroid. No laboratory parameters were found to be statistically significant; at baseline but after 28 days of treatment S. albumin showed significant P value between two groups (39.13±2.04 vs 37.24±5.94).

In this study, it was found that Rifaximin was able to decrease stool frequency to 1-2 times (67.3%); whereas Mesalamine was able to limit stool frequency to 3-4 times (80%) and >5 stools (13.3%). Tursi et al. (2010)found that Mesalamine also was unable to reduce bowel frequency significantly.[20] ASCEND II trial (2005) demonstrated that high dose Mesalamine (4.8 gm/d) is more effective (72%) than low dose (2.4 gm/d) Mesalamine (59%) during flare.[21]

By the physician's global assessment, Rifaximin was able to return the major portion of the participants to normal (20%) or mild disease status (45.5%). Moderately severe disease (40%) and severe disease (11.1%) were predominantly in Mesalamine group. Lorenzetti and Prantera (2013) reported several open label multicenter studies on Chrons disease and Ulcerative colitis where remission rate was 59-67% after 16-12 weeks of Rifaximin treatment.[22] Lichtenstein (2007) showed that treatment with Rifaximin 1600mg/dl had the highest clinical remission, clinical response and lowest rate of treatment failure than the placebo group.[23] Gawronska et al. (2017) found that Rifaximin group had the highest cure rate (78.6%).[24]

In this study hair fall and constipation were reported in both groups. But frequency of hair fall (75%) and constipation (42.60%) were prevalent in Mesalamine group. Sninsky et al. (1991) found that headache was the prevalent adverse reaction among the treatment group with Rifaximin.[25] But Muniyappa et al. (2009) found headache to be more frequent.[26]

Conclusion

Targeting microbial dysbiosis in ulcerative colitis patient Rifaximin has promising role in comparison to Mesalamine in ulcerative colitis patient with mild to moderate flare up. Moreover, high dose of Mesalamine sometimes can cause adverse events compared to Rifaximin. High dose and long term Rifaximin use has no negative impact on disease behavior, rather associated with significant improvement.

Conflict of Interest:

There is no conflict of interest of any authors in this study.

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