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THE ROLE OF PREBIOTICS AND PROBIOTICS IN ULCERATIVE COLITIS: A PLACEBO-CONTROLLED RCT

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Abstract
Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterized by mucosal inflammation of the colon. Emerging evidence suggests that modulation of the gut microbiota through prebiotics and probiotics may offer therapeutic benefits in UC management. This randomized, double-blind, placebo-controlled trial aimed to evaluate the efficacy of combined prebiotic and probiotic supplementation in inducing and maintaining remission in patients with mild to moderate UC. A total of 120 patients were randomized to receive either a synbiotic formulation containing inulin-type fructans and a multi-strain probiotic blend or a placebo, alongside standard mesalazine therapy, over 12 weeks. Clinical remission, assessed by the Mayo score, was achieved in 65% of the synbiotic group compared to 35% in the placebo group ($p=0.002$). Furthermore, significant reductions in fecal calprotectin levels and endoscopic scores were observed in the intervention group ($p<0.01$). No serious adverse events were reported. These findings indicate that adjunctive synbiotic therapy can enhance clinical outcomes in UC patients, potentially through modulation of gut microbiota and attenuation of mucosal inflammation. Further large-scale studies are warranted to confirm these results and elucidate underlying mechanisms.

Keywords: Ulcerative colitis, Synbiotics, Gut microbiota

Introduction

Ulcerative colitis (UC) is a chronic idiopathic inflammatory bowel disease (IBD) characterized by continuous mucosal inflammation of the colon, leading to symptoms such as diarrhea, rectal bleeding, and abdominal pain. The etiology of UC is multifactorial, involving genetic predisposition, environmental factors, immune dysregulation, and alterations in the gut microbiota.[1-3] Recent studies have highlighted the significant role of gut microbiota in the pathogenesis of UC. Dysbiosis, characterized by reduced diversity and imbalance of commensal bacteria, has been observed in UC patients, suggesting that restoration of microbial balance may be a therapeutic target.[4-7] Prebiotics, non-digestible food components that selectively stimulate the growth of beneficial bacteria, and probiotics, live microorganisms that confer health benefits to the host, have been investigated for their potential in modulating gut microbiota and ameliorating UC symptoms. Synbiotics, a combination of prebiotics and probiotics, may offer synergistic effects in restoring microbial balance and enhancing mucosal healing.[8]

Several randomized controlled trials (RCTs) have explored the efficacy of prebiotics, probiotics, and synbiotics in UC management. For instance, a study by Valcheva et al. demonstrated that β-fructan prebiotics reduced the severity of biochemical relapse in UC patients, although they did not prevent symptomatic relapses. Another study reported that 1-kestose, a fructooligosaccharide, provided clinical improvement in patients with mild to moderate UC through gut microbiome modulation.[9-10] Despite these findings, the clinical efficacy of synbiotic therapy in UC remains inconclusive, necessitating further well-designed RCTs to establish its role in inducing and maintaining remission.[11-13] This study aims to evaluate the efficacy and safety of a synbiotic formulation containing inulin-type fructans and a multi-strain probiotic blend in patients with mild to moderate UC.

Methodology

This study was a randomized, double-blind, placebo-controlled trial conducted over 12 weeks. At Department of gastroenterology and hepatology Sahiwal Teaching hospital Sahiwal. Eligible participants were adults aged 18 to 65 years with a confirmed diagnosis of mild to moderate UC, defined by a Mayo score of 3 to 10, and stable doses of mesalazine for at least four weeks before enrollment. Exclusion criteria included the use of antibiotics or probiotics within four weeks, corticosteroid use within two weeks, pregnancy, lactation, and significant comorbidities.

Sample size calculation was performed using Epi Info software, assuming a 30% difference in remission rates between the intervention and placebo groups, with a power of 80% and a significance level of 0.05. Accounting for a 20% dropout rate, a total of 120 participants were required.

Participants were randomized in a 1:1 ratio to receive either the synbiotic formulation or a placebo. The synbiotic comprised 10 g/day of inulin-type fructans and a probiotic blend containing Lactobacillus acidophilus, Bifidobacterium bifidum, and Streptococcus thermophilus, administered orally. The placebo group received a maltodextrin powder identical in appearance and taste.

Clinical assessments, including the Mayo score, fecal calprotectin levels, and endoscopic evaluation, were conducted at baseline and the end of the study. Adverse events were monitored throughout the study period. Verbal and written informed consent were obtained from all participants, and the study protocol was approved by the institutional ethics committee.

Results

Table 1: Baseline Demographic and Clinical Characteristics

Characteristic	Synbiotic Group (n=60)	Placebo Group (n=60)	p-value
Age (years), mean ± SD	38.5 ± 10.2	39.1 ± 9.8	0.72
Male, n (%)	32 (53.3%)	30 (50.0%)	0.71
Disease duration (years)	5.2 ± 2.1	5.4 ± 2.3	0.65
Baseline Mayo score	6.5 ± 1.2	6.4 ± 1.3	0.58

Table 2: Clinical Outcomes at Week 12

Outcome	Synbiotic Group (n=60)	Placebo Group (n=60)	p-value
Clinical remission, n (%)	39 (65.0%)	21 (35.0%)	0.002
Fecal calprotectin (µg/g), mean ± SD	150 ± 45	280 ± 60	<0.001
Endoscopic Mayo subscore ≤1, n (%)	42 (70.0%)	27 (45.0%)	0.005

Table 3: Adverse Events

Adverse Event	Synbiotic Group (n=60)	Placebo Group (n=60)	p-value
Mild gastrointestinal symptoms, n (%)	5 (8.3%)	4 (6.7%)	0.73
Serious adverse events, n (%)	0 (0%)	0 (0%)	N/A

The synbiotic group demonstrated a significantly higher clinical remission rate and greater reductions in fecal calprotectin levels compared to the placebo group. Endoscopic improvement was also more pronounced in the synbiotic group. Adverse events were mild and comparable between groups.

Discussion

The results of this randomized, double-blind, placebo-controlled trial indicate that adjunctive synbiotic therapy significantly enhances clinical remission rates and reduces inflammatory markers in patients with mild to moderate UC. The synbiotic formulation, comprising inulin-type fructans and a multi-strain probiotic blend, was well-tolerated and did not result in serious adverse events.[14-17]

These findings align with previous studies suggesting the beneficial effects of prebiotics and Probiotics in UC management. For instance, Valcheva et al. reported that β-fructan prebiotics reduced the severity of biochemical relapse in UC patients, although they did not prevent symptomatic relapses. Similarly, a study on 1-kestose demonstrated clinical improvement in UC patients through gut microbiome modulation.[18]

The observed reduction in fecal calprotectin levels and endoscopic scores suggests that synbiotic therapy may attenuate mucosal inflammation, potentially through modulation of the gut microbiota and enhancement of the intestinal barrier function. This is supported by evidence indicating that probiotics can suppress pathogen growth, modulate immune responses, and enhance barrier activity.[19-20]

While the study provides compelling evidence for the efficacy of synbiotic therapy in UC, certain limitations must be acknowledged. The relatively short duration of the study may not capture long-term outcomes, and the exclusion of patients with severe UC limits the generalizability of the findings. Further large-scale, long-term studies are warranted to confirm these results and explore the underlying mechanisms. The significant improvement observed in the clinical outcomes of patients receiving synbiotics in this study aligns with the growing body of research highlighting the role of gut microbiota in inflammatory bowel diseases (IBD), including UC. The concept of microbial dysbiosis—where the balance of gut microbiota is disturbed—has been well-documented in UC

patients, and evidence suggests that restoring the microbiota balance through prebiotics and probiotics may contribute to disease management.[21-22]

Prebiotics, such as inulin-type fructans, have been shown to selectively stimulate the growth of beneficial gut bacteria, thereby fostering a healthy microbiome environment. This can result in enhanced mucosal barrier integrity and immune modulation, both of which are critical in managing UC. The synbiotic combination used in this study may have led to increased levels of beneficial bacteria such as Lactobacillus and Bifidobacteria, which are known to have anti-inflammatory properties. These effects likely played a role in the significant reductions in fecal calprotectin levels and the improvement in endoscopic findings observed in the synbiotic group.[23]

Probiotics, as part of the synbiotic formulation, have been associated with immunomodulatory effects that can help reduce colonic inflammation. Studies have demonstrated that certain strains of probiotics, particularly those in the Lactobacillus and Bifidobacterium genera, can enhance the production of anti-inflammatory cytokines and suppress pro-inflammatory mediators, such as TNF-α and IL-6, which are elevated in UC patients. The combination of probiotics and prebiotics may therefore have acted synergistically to induce and maintain remission in the patients enrolled in this trial.[24-25]

Interestingly, the placebo group did not show significant improvements in clinical remission or reduction in inflammatory markers, suggesting that mesalazine alone may not have been sufficient to induce substantial improvement in patients with mild to moderate UC. This further supports the potential role of synbiotics as an adjunctive therapy to conventional treatments.

It is important to note that the study also demonstrated a relatively low incidence of adverse events, further confirming the safety of the synbiotic intervention. Mild gastrointestinal symptoms were reported by a small proportion of participants, consistent with findings from other studies on probiotics, but these were transient and resolved without any significant clinical consequences. No serious adverse events were observed in either group, indicating that synbiotics, when used as adjunctive therapy, are well-tolerated.

The results of this trial are consistent with those of previous studies, which have indicated positive effects of synbiotics on UC. However, this study is unique in its use of a multi-strain probiotic formulation combined with inulin-type fructans, and its focus on patients with mild to moderate UC, who are typically underrepresented in clinical trials. The findings contribute to the growing evidence supporting the use of synbiotics as a complementary treatment option in UC management.

Despite the promising results, several limitations to this study warrant consideration. Firstly, the study duration was limited to 12 weeks, which may not have been sufficient to assess long-term outcomes and sustained remission. Additionally, the study excluded patients with severe UC, which limits the applicability of these results to more advanced cases of the disease. Future studies with a longer follow-up period and inclusion of patients with severe UC are necessary to determine the long-term efficacy and safety of synbiotics in UC management. Furthermore, while the study demonstrated significant improvements in clinical remission and inflammatory markers, it did not assess the direct mechanisms by which synbiotics exert their effects, such as changes in the gut microbiota composition or immune function. This would be an important area of investigation in future studies.

Conclusion

In conclusion, the results of this randomized, double-blind, placebo-controlled trial suggest that synbiotic therapy, consisting of inulin-type fructans and a multi-strain probiotic blend, is a safe and effective adjunctive treatment for patients with mild to moderate ulcerative colitis. The synbiotic formulation significantly improved clinical remission rates, reduced inflammatory markers, and enhanced endoscopic outcomes, without major safety concerns. These findings support the incorporation of synbiotics into the therapeutic regimen for UC patients, particularly as an adjunct to standard medical therapies. Further long-term, large-scale studies are needed to confirm these results and explore the underlying mechanisms of action. Additionally, future research should investigate the efficacy of synbiotics in more severe forms of UC and assess their impact on the long-term health of patients.

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