

# Effects of synbiotic therapy in mild-to-moderately active ulcerative colitis: A randomized placebo-controlled study

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## ABSTRACT

**Background/Aims:** Recently, there has been an increasing interest in the effects of probiotics and prebiotics on ulcerative colitis (UC). In the present study, we aimed to evaluate the effect of synbiotic therapy on the clinical and endoscopic activities of the disease in patients with mild-to-moderately active UC.

**Materials and Methods:** Overall, 40 patients with mild-to-moderate UC activity were included in the study and were randomized to the synbiotic and control groups. Synbiotic therapy was administered in the synbiotic group and placebo was administered in the control group for 8 weeks. Both groups were evaluated and compared in terms of the acute phase reactants and clinical and endoscopic activities of the disease at the beginning and at the end of the 8-week therapy.

**Results:** At the end of the study duration, the decrease in the serum C-reactive protein (CRP) and sedimentation values in the synbiotic group was statistically significant ( $p=0.003$ ). In both groups, a statistically significant improvement was observed in the clinical and endoscopic activity levels at the end of the treatment (synbiotic:  $p=0.001$  and  $p=0.002$ , respectively; control:  $p=0.005$  and  $p=0.001$ , respectively). When the groups were compared with each other, improvement in the clinical activity was significantly higher in the synbiotic group ( $p<0.05$ ).

**Conclusion:** The use of synbiotic therapy in patients with UC has a significant effect on the improvement in clinical activity. Moreover, although it appears to positively affect the acute phase reactants and endoscopic activity levels, the difference was not significant when compared with the patients who did not receive synbiotic therapy.

**Keywords:** Ulcerative colitis, synbiotic, prebiotic, probiotic

## INTRODUCTION

Ulcerative colitis (UC) is an idiopathic inflammatory disease of the intestine, presenting with typical symptoms, such as rectal bleeding, bloody and mucous diarrhea, and abdominal pain, and it is characterized by relapse and remission periods (1). In recent years, the prevalence and incidence of UC have begun to increase depending on age, gender, ethnic characteristics, geographical location, and socioeconomic conditions, and it has emerged as a global health problem (2,3).

Although the etiology and pathogenesis of the disease are not exactly known, it is considered to be associated with certain infectious agents, nutrients, environmental factors, and genetic disorders (4). In recent years, there has been a particularly increasing interest in the effect of nutrition on the etiology of the disease; according to a hypothesis, UC in individuals with genetic susceptibility is considered to originate from the uncontrolled immune

response developing against intestinal microbiota. Therefore, it is particularly argued that bad eating habits trigger the onset of the disease and affect its progression and course (5,6).

Probiotics and prebiotics positively affect the health of the host by regulating the microbial balance in the intestine, and they may repair damaged intestinal microbiota in UC (7). It is argued that the beneficial effects of probiotic bacteria in inflammatory bowel diseases occur by inhibiting the colonized proliferation of pathogenic microorganisms in the colon and strengthening the host immune system and the mucosal barrier system. Furthermore, it has been reported in the studies that probiotics decrease the secretion of proinflammatory cytokines and have anti-inflammatory effects (8). Prebiotics affect the increase in the number and activity of probiotics and extend their lifespan (7). Based on these effects, many studies on the activities of probiotics and prebiotics in UC have recently

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been carried out. On the other hand, the number of studies on the effects of synbiotics, which contain both probiotics and prebiotics together, in UC is quite limited.

This study is a randomized placebo-controlled study that evaluated the effects of synbiotic therapy in addition to the medical treatment in patients with mild-to-moderately active UC.

## **MATERIALS AND METHODS**

### **Patient selection**

A total of 40 patients with UC aged 18 years and older with mild-to-moderate disease activity, who were previously or newly diagnosed by clinical, endoscopic, or histopathological findings between April 2016 and June 2017, were included in the study. The clinical activity was determined using the Truelove-Witts Clinical Activity Index, and the endoscopic activity was determined using the ulcerative colitis endoscopic index of severity (UCEIS).

Patients who showed a severe disease activity clinically and endoscopically, who were administered corticosteroids or biological therapy 4 weeks before the study, who were found to have a concurrent enteric infection, who used probiotic and/or synbiotic preparations and antibiotics 2 weeks before the study, pregnant and breastfeeding women, patients with end-stage liver and renal failure, and those with sensitivity to probiotics and/or synbiotics were excluded from the study. Patients who needed a change in their medical treatment during the 8-week study period, those who did not comply with the study protocol and were not cooperating, and those who did not want to continue the study voluntarily were also excluded from the study.

### **Study design**

Patients were randomized into two groups -the synbiotic and control group- using the Random Allocation Software program. For 8 weeks, placebo for the control group and the synbiotic chewable tablets for the synbiotic group were administered as one tablet after breakfast and dinner. The synbiotic preparation was composed of six probiotic strains ( $3 \times 10^9$  CFU)-*Enterococcus faecium*, *Lactobacillus plantarum*, *Streptococcus thermophilus*, *Bifidobacterium lactis*, *Lactobacillus acidophilus*, *Bifidobacterium longum*-and fructooligosaccharide (225 mg/tablet), which is a prebiotic fiber. The placebo product had the same taste and appearance as the original product. The synbiotic (NBL Probiotic Optima) and placebo products were produced by the Nobel Pharmaceutical Company, Istanbul, Turkey.

The hemoglobin, leukocyte, neutrophil-to-lymphocyte ratio, sedimentation, and C-reactive protein (CRP) values and clinical and endoscopic activity indices of patients were evaluated at the beginning of the study and at the end of 8 weeks. Sedimentation was measured by the quantitative capillary photometry method, and the CRP was measured by the immuno-turbidimetric method, with 20 parameters on the hemogram blood count autoanalyzer.

The post-hoc power analysis of the study was calculated using the results comparing pre- and post-sedimentation values of the study group (study group before  $36.44 \pm 30.68$  mm/sec and after  $20.67 \pm 17.76$  mm/sec). When the sample number was considered as 18 with an effect size of 0.79 and an error margin of 0.05, the power of the study was found to be 0.87 (correlation between measurements, 0.79).

### **Statistical analysis**

Study results were evaluated using the Statistical Package for Social Sciences version 22.0 (IBM Corp.; Armonk, NY, USA) for Windows package program (9). The per-protocol analysis was adopted in the analysis of all data in the study. The Shapiro-Wilk test was used to determine whether continuous data primarily showed normal distribution. The paired sample t-test (dependent sample t-test) was used in the comparison of normally distributed and repetitive quantitative data of both groups, Student's t-test was used in the comparison of normally distributed and non-repetitive data, and the Mann-Whitney U test was used in the comparison of non-normally distributed and non-repetitive data. The chi-squared ( $\chi^2$ ) analysis was applied to determine the relationship between categorical variables. The Wilcoxon paired two-sample test was performed in the intragroup comparison of quantitative data of the control and study groups (before and after). A p-value of  $<0.05$  were considered statistically significant.

## **RESULTS**

During the study period, one of the patients in the control group voluntarily left the study on the grounds that there was an increase in the number of stools, and one patient was excluded from the study because he did not come to examinations at the end of the study. In the synbiotic group, one patient voluntarily left the study because of bloating issues, and other patient voluntarily left the study because he did not want to continue to use the product. In conclusion, the study was evaluated over the findings of 18 patients in both groups. Figure 1 illustrates a flow chart of participants through the study protocol.

Overall, 10 male and 8 female patients were included in the control group, and 9 male and 9 female patients were included in the synbiotic group. The average age of pa-

tients was 40.00±12.67 years and 44.94±14.14 years in the control and synbiotic groups, respectively. On examining the location of the disease, 55.6% of patients in the control group had extensive colitis and 44.4% of patients in the synbiotic group had distal colitis. Mean of the number of years since disease diagnosis was 4.58±4.39 years in the control group and 4.67±6.23 years in the synbiotic group. The vast majority of patients in both groups were treated with mesalazine alone (control group 61.1% and synbiotic group 88.9%). Seven patients in the control group and two patients in the synbiotic group were treated with a mesalazine and azathioprine combination. Mean duration of azathioprine therapy was 24.4±21.8 months in the control group and 20.5±13.4 months in the synbiotic group (p=0.8). Overall, 55.6% of patients in the control group and 44.4% in the synbiotic group had a comorbid disease. Furthermore, 44.4% of the individuals in the control group and 33.3% of patients in the synbiotic group were using medications for these comorbid diseases. No statistically significant difference were found between the two groups in terms of all these findings. The findings are summarized in Table 1.

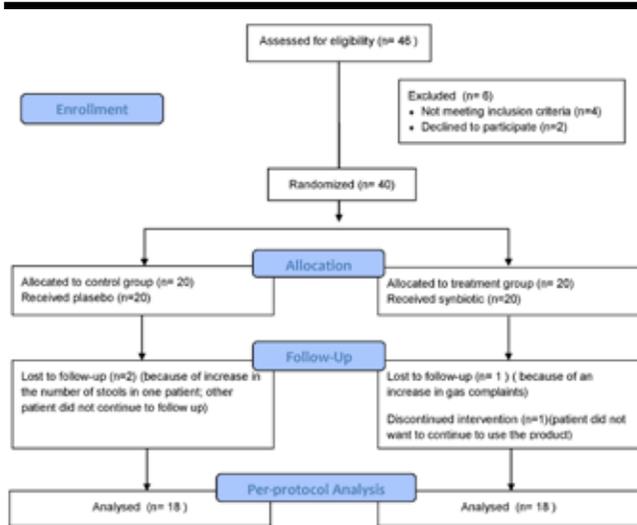


Figure 1. Flow diagram of the randomized-controlled trial

Table 1. General characteristics of the control and synbiotic groups

General Characteristics	Control Group (n=18)		Synbiotic Group (n=18)		p <sup>x</sup>
	n	%	n	%	
<b>Gender</b>					
Female	8	44.4	9	50.0	0.999
Male	10	55.6	9	50.0	
Duration of UC (year, $\bar{X}\pm SD$ )	4.58±4.39		4.67±6.23		0.524 <sup>y</sup>
Age (year) ( $\bar{X}\pm SD$ )	40.00±12.67		44.94±14.14		0.277 <sup>z</sup>
<b>Type of UC</b>					
Extensive colitis	10	55.6	5	27.8	0.139
Proctitis	3	16.6	8	44.4	
Left-sided colitis	5	27.8	5	27.8	
<b>Medical Treatments for UC</b>					
Mesalazine	11	61.1	16	88.9	0.121
Mesalazine and Azathioprine	7	38.9	2	11.1	
<b>Comorbid Diseases</b>					
Diabetes mellitus	-	-	1	11.1	NA
Cardiovascular disease	1	10.0	5	55.6	
Gastrointestinal system disease	2	20.0	1	11.1	
Respiratory system disease	2	20.0	-	-	
Other	5	50.0	2	22.2	

UC: ulcerative colitis

<sup>x</sup>Pearson's chi-square ( $\chi^2$ ) and Fisher exact test were used for comparison (p<0.05)

<sup>y</sup>Mann-Whitney U test was used for comparison of UC duration (p<0.05)

<sup>z</sup>Student's t-test was used for age comparison (p<0.05)

**Table 2.** Comparison of biochemical parameters between the groups at the beginning and end of the study

Biochemical Parameters	Control Group (n=18)			Synbiotic Group (n=18)			p <sup>y</sup>	p <sup>z</sup>			
	Baseline		Week 8	Baseline		Week 8					
	$\bar{X} \pm SD$	Changes (%)	SD	$\bar{X} \pm SD$	Changes (%)	SD					
Hemoglobin (g/dL)	12.9±1.9	13.4±1.4	5.5	15.8	0.184	12.8±1.9	13.0±1.6	2.9	12.5	0.448	0.476
Leukocyte (BIN/m <sup>3</sup> )	8.3±2.4	7.7±2.2	-3.9	21.9	0.500	7.6±1.6	7.4±1.9	-1.3	36.1	0.286	0.924
Platelets (BIN/m <sup>3</sup> )	316.7±147.2	291.0±91.2	-3.5	16.7	0.500	329.9±134.6	297.3±111.4	-6.5	15.9	0.081	0.506
Neutrophil (BIN/m <sup>3</sup> )	4.7±1.6	4.8±1.5	5.6	31.3	0.983	4.2±1.2	4.5±1.7	13.8	56.9	0.687	0.752
Lymphocyte (BIN/m <sup>3</sup> )	2.2±0.7	1.9±0.7	-7.5	22.3	0.057+	2.2±0.6	2.1±0.6	-4.9	19.9	0.176+	0.849
Neutrophil-to-lymphocyte rate	2.3±0.69	2.8±1.58	25.8	71.2	0.396	2.08±0.93	2.3±0.96	25.5	72.6	0.948	0.752
CRP (mg/dL)	0.5±0.4	0.7±1.6	200.2	605.8	0.170	0.9±1.0	0.6±0.8	-48.2	47.9	0.003	0.051
Sedimentation (mm/hour)	13.0±7.6	14.3±13.0	2.1	55.9	0.740	36.4±30.7	20.7±17.8	-28.4	33.7	0.003	0.137

\*Wilcoxon test; +Paired samples test (p&lt;0.05)

<sup>x</sup>The difference before and after 8 weeks in the control group<sup>y</sup>The difference before and after 8 weeks in the synbiotic group<sup>z</sup>Mann-Whitney U test was used for comparison (p<0.05)

### Changes in laboratory parameters

The laboratory parameters of the control and synbiotic groups at the beginning and at the end of the study, and the extent of change within 8 weeks, are presented in Table 2. Changes in the hemoglobin, leukocyte, neutrophil, lymphocyte, and thrombocyte levels and the neutrophil-to-lymphocyte ratio of patients from both groups at the end of the study were not significant. Although the change in the CRP and sedimentation values at the beginning and after treatment was not significant in the control group, a statistically significant decrease was observed in the synbiotic group (-48.18±47.99% and -28.39±33.71%, respectively; p=0.003). When both groups were compared between each other, it was observed that there was no significant difference in changes between the groups (p=0.051 and p=0.137, respectively).

### Changes in the clinical and endoscopic activities of the disease

According to the Truelove-Witts Clinical Activity Index, the majority of patients (83.3%) in the control group showed mild disease activity at the beginning of the study, and 61.1% of them also showed mild activity at the end of the study. A total of 33.3% of patients were in the clinically remission, and this change in the disease activity was statistically significant (p=0.005). In the synbiotic group, the majority of patients (66.7%) had moderate disease activity at the beginning. It was determined that the majority of patients (55.6%) had remission at the end of the study, 33.3% of them remained in the mild disease activity, and these changes were statistically significant (p=0.001; Table 3).

According to the UCEIS, although one-half of patients in the control group had mild disease activity and the other half had moderate disease activity at the beginning, it was observed that 44.4% of patients reached endoscopic remission at the end of the study, 38.9% of them remained in the mild activity, and these changes were also significant (p=0.002). The majority of patients in the synbiotic group (61.1%) showed moderate activity at the beginning of the study according to the UCEIS, and it was determined that the majority (55.6%) of them reached remission; this change was statistically significant (p=0.002; Table 3). When the UCEIS scores of patients in the control and synbiotic groups at the beginning and end of the study were compared, it was observed that there was a significant decrease in the scores both in the control group and the study group. The mean UCEIS score of patients in the control group was 4.6±1.0 and 2.3±1.6 at the beginning of the study and at the end

**Table 3.** Evaluation of the clinical and endoscopic activities in the control and synbiotic groups at the beginning and end of the study

Disease Activity	Control Group (n=18)				p <sup>x</sup>	Synbiotic Group (n=18)				p <sup>y</sup>
	Baseline		Week 8			Baseline		Week 8		
	n	%	n	%		n	%	n	%	
Truelove-Witts Clinic Activity Index										
Remission	-	-	6	33.3	0.005	-	-	10	55.6	<0.001
Mild	15	83.3	11	61.1		6	33.3	6	33.3	
Moderate	3	16.7	1	5.6		12	66.7	2	11.1	
UCEIS										
Remission	-	-	8	44.4	0.002	-	-	10	55.6	0.002
Mild	9	50.0	7	38.9		7	38.9	4	22.2	
Moderate	9	50.0	3	16.7		11	61.1	4	22.2	
UCEIS Score, $\bar{X} \pm SS$										
	4.6±1.0		2.3±1.6		0.001	4.5±1.0		2.1±2.1		0.001
UCEIS Score Changes %										
	-151.4±154.35					-164.3±172.68				0.965 <sup>z</sup>

UCEIS: ulcerative colitis endoscopic index of severity

\*Wilcoxon test was used for comparison (p<0.05)

<sup>x</sup>The difference before and after 8 weeks in the synbiotic group

<sup>y</sup>The difference before and after 8 weeks in the control group

<sup>z</sup>Mann-Whitney U test was used for comparison between groups (p<0.05)

**Table 4.** Evaluation of the changes in the clinical and endoscopic activities of the patients at the end of the study

Changes in Clinical and Endoscopic Activities	Control Group (n=18)		Synbiotic Group (n=18)		p
	n	%	n	%	
Changes in Truelove-Witts Clinic Activity Index					
No change	10	55.6	2	11.1	0.005
From mild to remission	6	33.3	6	33.3	0.999
From moderate to mild	2	11.1	6	33.3	0.109
From moderate to remission	-	-	4	22.3	0.034
Changes in UCEIS					
No change	7	38.8	5	27.8	0.478
From mild to remission	5	27.8	5	27.8	0.999
From moderate to mild	3	16.7	3	16.6	0.999
From moderate to remission	3	16.7	5	27.8	0.424

\*The difference between two proportions (p<0.05). UCEIS: ulcerative colitis endoscopic index of severity

of the study, respectively. The score in the study group similarly decreased from 4.5±1.0 to 2.1±2.1 (p=0.001). When both groups were compared to each other, it was observed that there was no significant difference in the UCEIS score changes between the groups (p=0.965; Table 3).

Data on changes in the clinical and endoscopic activities during the study were evaluated by looking at the difference between the two ratios (Table 4). There was no change in the Truelove-Witts Clinical Activity Index of

diseases of the majority of patients (55.6%) in the control group. It was determined that the number of patients with a change in clinical activities was significantly higher in the synbiotic group compared to the control group (p=0.005). Although the number of patients whose clinical activity changed from mild to remission was equal in both groups, it was observed that the disease decreased from the moderate to the mild activity level only in the synbiotic group patients. Although there was no patients whose disease improved from the moderate activity to remission in the control group, 22.3% of patients in the

synbiotic group (n=4) showed an improvement from the moderate activity to remission. These ratios between the two groups were found to be significantly different ( $p=0.034$ ).

At the end of the study, there was no change in the endoscopic activities of seven patients in the control group and five in the synbiotic group according to the UCEIS ( $p=0.478$ ). It was determined that the number of patients whose condition improved from the mild activity to remission and moderate to mild endoscopic activities in both the control and synbiotic groups were equal ( $p=0.999$ ). The number of patients whose condition changed from the moderate activity to remission was higher in the synbiotic group compared to the control group; however, no statistically significant difference was found between the changes in the endoscopic activities of the control and synbiotic groups ( $p=0.424$ ).

## DISCUSSION

The number of studies investigating the effects of synbiotic supplements in patients with UC on the acute phase reactants and the clinical and endoscopic activities of the disease is quite limited. A large part of studies on UC colitis was carried out to determine the effects of probiotics on proinflammatory cytokines (TNF- $\alpha$ , IL-1, IL-6, etc.). In the majority of these studies, the measurement of proinflammatory cytokines was performed especially in the colon tissue culture (10-13). A randomized controlled study by Cui et al. (10) investigated effects of a probiotic supplement on the intestinal mucosa of patients with UC, and a significant decrease in the binding capacity of NF- $\kappa$ B to DNA and in the TNF- $\alpha$  level was reported in the probiotic group; moreover, a significant decrease was observed in the IL-1 $\beta$  expression and the colonic concentration of IL-6 in the probiotic group, whereas there was an increase in the anti-inflammatory cytokine IL-10 expression. Another study showed that yogurt enriched with probiotics significantly reduced the serum IL-12 concentrations in inflammatory bowel disease (IBD), but that it had no effect on the TNF- $\alpha$  and IL-10 concentrations (12). In a recent study by Senol et al. (14), the effectiveness of kefir in rats with experimental colitis was evaluated. It was reported that there was no statistically significant difference in the IL-10 levels between the groups, but that kefir treatment significantly reduced TNF- $\alpha$  in colitis-induced rats.

Two studies investigating the effect of the synbiotic use on the indicators of inflammation were found in the literature, similar to the present study. In the study carried

out by Furrie et al. (15), a synbiotic (*B. longum* and Synergy 1) was administered to the treatment group with active UC for 1 month, and maltodextroses tablet with potato starch were given to the control group. The proinflammatory cytokines, TNF- $\alpha$  and IL-1 $\alpha$ , significantly decreased in the colon tissue in the treatment group, whereas no significant difference was found in the immunomodulator cytokine IL-10 compared to the control group at the end of the study. Moreover, the CRP levels decreased in the synbiotic group, after 4 weeks of therapy. In the second study, the effectiveness of probiotic (*B. longum*), prebiotic (psyllium), and synbiotics was examined in patients with UC. At the end of the study, it was observed that the decrease in the CRP levels occurred mostly in the synbiotic group (16).

In the present study, only the acute phase reactants were used to evaluate inflammation. An insignificant decrease was observed in the leukocyte concentration in both groups. Although no significant change was observed in the CRP and sedimentation values in the control group, post-treatment values were found to be significantly lower than the pre-treatment values in the synbiotic group. These results supported the opinion that synbiotic therapy could be effective in preventing the exacerbations of patients with mild-to-moderately active UC and in improving the inflammation.

There are many studies in the literature investigating the effect of the probiotic and prebiotic use on the clinical and endoscopic activities of the disease in patients with active UC. The UCDAI has been generally used to evaluate the clinical activity of disease in the studies carried out with VSL#3 (*L. paracasei*, *L. plantarum*, *L. acidophilus*, *L. delbrueckii*, *B. longum*, *B. breve*, *B. infantis*, and *Streptococcus thermophilus*). Bibiloni et al. (17) reported that 53% of patients with mild-to-moderately active UC who did not respond to conventional treatment entered the remission after the VSL#3 therapy. In another study, it was observed that the number of patients with a 3-point or higher decrease in the UCDAI score was significantly greater in the group using VSL#3 among patients with mild-to-moderately active UC. At the end of this study, it was determined that 42.9% of the VSL#3 group and 15.7% of the control group reached remission ( $p<0.001$ ) (18). Similarly, Tursi et al. (19) determined that the number of patients with a significant decrease of 50% or more in the UCDAI score was higher in patients using VSL#3 compared to placebo in patients with mild-to-moderately active UC. In the study by Kato et al. (20), which included patients with mild-to-moderate UC using 5-ASA

or sulfasalazine, it was observed that the response rate of treatment was 70% in the bifidobacteria-fermented milk group and 33% in the placebo group and that remission was 40% in the BMF group and 33% in the placebo group based on the clinical activity index (CAI) at the end of the study. A further decrease was also observed in the CAI mean score compared to the placebo group.

Most commonly used prebiotics in the studies are lactulose, inulin, FOS, and malt. It was determined that malt provided a significant decrease in the CAI scores (21-24). Furthermore, it was also observed that the endoscopy index score significantly decreased after the therapy (24). In a pilot study, which examined the effect of lactulose on IBD, it was observed that lactulose decreased the CAI score of patients by  $5.6 \pm 2.3$  and that 4 of 7 patients entered remission (25). In another study, placebo (maltodextrin) and inulin were compared in patients with mild-to-moderately active UC using mesalazine. At the end of the study, the Rachmilewitz score was found to be significantly lower in the inulin group compared to the placebo group (26).

The number of studies examining the effects of synbiotics on the clinical and endoscopic activities of the UC is quite limited compared to probiotics and prebiotics. In a randomized controlled pilot study conducted in patients with active UC, although synbiotic (*B. longum* and FOS/inulin) provided an average decrease of 1.3 points in the sigmoidoscopy score, it was observed that placebo caused an increase of 0.58 points. The sigmoidoscopy scores were significantly further decreased in the synbiotic group (at the beginning 4.5 [1.4] and at the end 3.1 [2.5]) compared to the placebo (at the beginning 2.6 [2.1] and at the end 3.2 [2.2]). There was no significant difference determined between the CAI scores (15). Similarly, in another study carried out by Ishikawa et al. (27), it was determined that there was a significant improvement in the endoscopic activity in the group using fermented milk (kefir) and galactooligosaccharide compared to the placebo group.

In the present study, the Truelove-Witts Clinical Activity Index and UCEIS were used to determine the effect of the synbiotic use on the clinical and endoscopic activities of the disease. At the end of the study, it was observed that, compared with the control group, a higher number of patients in the synbiotic group entered remission, according to the Truelove-Witts Clinical Activity Index (55.6% and 33.3%). Furthermore, it was determined that the number of patients who did not respond to treatment (55.6%)

was significantly higher in the control group than the synbiotic group (11.1%). Significant improvement was observed in the UCEIS similar to the clinical activity in both groups. Although the ratio of patients entering remission was found to be higher in the synbiotic group according to the UCEIS (55.6% and 44.4%, respectively), this difference was not found to be statistically significant. On evaluating the changes in the UCEIS scores, it was observed that the scores significantly decreased at the end of the study in both groups. This decrease was greater in the synbiotic group; however, the difference between the groups was not statistically significant.

There are some limitations to our study. The main limitations are the small number of patients included and the absence of more specific and objective markers of inflammation, such as histologic scores and fecal calprotectin.

In conclusion, it can be said that the use of synbiotics in addition to medical treatment in UC significantly affects the improvement in the clinical activity. It has also positive effects on improvement in the endoscopic activity and on decrease in acute phase reactants; however, these effects are not significantly different compared to those in individuals who do not use synbiotics.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the Akdeniz University School of Medicine Clinical Research Ethics Committee (Decision Number: 175, Decision Date: 09.03.2016).

**Informed Consent:** Written informed consent was obtained from the patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

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