A Randomized, Double-blind, Placebo-controlled Multicenter Trial of *Saccharomyces boulardii* in Irritable Bowel Syndrome

Effect on Quality of Life

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Background: Probiotics confer health benefits to the host. However, its clinical effect on irritable bowel syndrome (IBS) is controversial.

Aims: This study was aimed to evaluate the effects of *Saccharomyces boulardii* on quality of life (QOL) and symptoms in patients with diarrhea-predominant IBS or mixed-type IBS.

Methods: Sixty-seven patients with IBS were randomized either to receive *S. boulardii* at 2×10^{11} live cells as a daily dose (n = 34), or placebo (n = 33) for 4 weeks. IBS-QOL was assessed at the beginning and end of the treatment phase. IBS-related symptoms, bowel movement frequency, and stool consistency were recorded on a daily basis and assessed each week.

Results: The overall improvement in IBS-QOL was higher in *S. boulardii* group than placebo (15.4% vs 7.0%; $P < 0.05$). All eight domains of IBS-QOL were significantly improved in *S. boulardii* group; however, placebo group only showed improvements in dysphoria and health worry. Composite scores for IBS symptoms were significantly reduced in both groups to a similar extent. Bowel frequency and stool consistency did not change in either group.

Conclusions: *S. boulardii* improved IBS-QOL better than placebo but was not superior for individual symptoms in patients with diarrhea-predominant IBS or mixed-type IBS.

Key Words: irritable bowel syndrome, probiotics, quality of life

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Irritable bowel syndrome (IBS) is a common disorder characterized by persistent or recurrent abdominal pain and discomfort with altered bowel habits. It affects approximately 10% to 20% of the adult population, and typical symptoms are abdominal pain, constipation, diarrhea, and bloating.[1–3] IBS is not lethal; however, can reduce quality of life (QOL) and increase medical costs. Several mechanisms for symptoms have been proposed, including a disturbed intestinal motility, visceral hypersensitivity, abnormal brain-gut interaction, and autonomic nervous system abnormalities.[4–8] IBS might be caused by changes in intestinal flora, intestinal infection, and activation of the mucosal immune system.[9–13]

Probiotics are nonpathogenic microorganisms that give health benefits to the host.[14] Lactobacilli, bifidobacteria, and nonpathogenic yeasts, such as *Saccharomyces boulardii*, are the most common probiotics and may influence gastrointestinal disorders including acute infectious diarrhea, inflammatory bowel diseases, allergic disorders, and IBS.[15] Probiotics competitively inhibit pathologic bacteria and abnormal fermentation, synthesize antibacterial substances, prevent bacterial translocation, enhance gut barrier function, and modulate signaling pathways in the mucosal immune system.[16–21] However, few randomized controlled trials have tested the efficacy of probiotics for IBS and the results were controversial.[22] The aims of this study were to evaluate the effects of *S. boulardii* on QOL and symptoms in patients with IBS.

MATERIALS AND METHODS

Patients

We recruited patients with IBS at Chung-Ang University Hospital, Gangnam Severance Hospital, and Asan Medical Center from September, 2006, until April, 2007. Diagnosis of IBS was based on Rome II criteria; at least 12 weeks (which do not need to be consecutive) in the preceding 12 months of abdominal discomfort or pain that has 2 of 3 features: relieved by defecation and/or associated changes in stool frequency and/or stool consistency. The study was carried out in patients with diarrhea-predominant type IBS (IBS-D) or mixed-type IBS (IBS-M) but excluding constipation-predominant IBS.[3] The inclusion criteria were: men or women aged between 20 and 65 years; organic abnormality excluded by blood chemistry and colonoscopy performed during the screening period; and signed written informed consent. Women of reproductive age were verified as not pregnant and used contraception during the study. Exclusion criteria included intolerance to yeasts or lactose; pregnancy or lactation; severe systemic illness (liver cirrhosis, congestive heart failure, chronic renal

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failure, angina, uncontrolled hypertension, endocrine disorder, metabolic disorder, malignant tumors); concurrent psychiatric disorder; previous abdominal surgery other than appendectomy and abdominal wall hernia repair; history of other clinical trial within 3 months before onset of this trial; use of drugs influencing the evaluation of efficacy during study period; and the patients judged ineligible by a clinician. The study protocol was approved by the ethics review committee of each hospital.

Randomization of Treatment Group or Placebo Group and Administration of Drug

This study used randomized allocation. Patients who met inclusion criteria and consented to participation were randomly allocated to treatment or placebo groups according to a blocked randomization allocation sequence. Patients received Bioflor (Kuhnil, Seoul, Republic of Korea; *S. boulardii* at 2×10^{11} live cells) or matching placebo, 2 capsules twice daily, orally for 4 weeks. The investigators and the patients were blinded to the assignment. Compliance was calculated as percentage of planned ingestion of the study product, and a compliance rate above 80% was set as minimum.

Progress of Clinical Trials

Patients who fulfilled the inclusion criteria by means of a clinical history, physical examination, drug use, colonoscopy, and blood tests were evaluated by IBS-QOL and recorded symptoms, bowel movement frequency, and stool consistency on a daily basis for 1 week before study initiation. The symptoms, adverse effects, bowel movement frequency, and stool consistency were recorded daily during the study period, and QOL was assessed after 4 weeks. Patients visited the study unit to receive the investigational products and to assess compliance, symptoms, and safety at every 2 weeks after first administration. After the treatment period, in cases of abnormal laboratory tests, patients made another visit within 2 weeks to assess adverse effects and for final safety evaluation.

Efficacy Measures

The primary efficacy variable was the difference in QOL after 4-week treatment using the IBS-QOL questionnaire, evaluated as the percentage of change in scores. QOL assessment was performed using the Korean version of Irritable Bowel Syndrome Quality of Life developed by Patrick et al.[23,24] The instrument contains 34 items scored from 1 to 5 to derive 8 subscale scores (dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual, and relationships) transformed to a scale of 0 to 100, with 100 representing the best possible QOL. We also evaluated changes in 10 symptoms related to IBS (abdominal pain, discomfort, hard/lumpy stool, loose/watery stool, straining, urgency, sense of incomplete evacuation, mucus in stool, bloating, passage of gas) for 5 weeks (1 wk baseline and 4 wk treatment) as secondary efficacy variables. Patients recorded daily symptoms using the 7-point Likert scale (ranging from 0 to 6), and the changes of weekly mean scores were measured. We also assessed the frequency (number per day) and the consistency of stools using the Bristol stool Scale, which ranges from 1 to 7 and a high score indicates looser stool. Safety assessments were performed at least once through follow-up in both groups of patients.

Statistical Analyses

SPSS Window version 13.0 was used to perform all data analyses. Categorical variables were compared with the χ^2 test, and continuous variables were compared with Student t test for clinical characteristics. We used the paired t test to compare primary and secondary efficacies within groups, and Student t test to compare the percentage of change before and after administration between the 2 groups. Differences in the incidence of adverse events were analyzed using Fisher exact test in safety assessment. The data are expressed as mean ± SD, and statistical significance was determined at $P < 0.05$.

RESULTS

Baseline Characteristics

Ninety-four patients entered the screening phase of the study (mean age 41 y; 48 female patients) (Fig. 1). Of these, 90 patients (mean age 41 ± 13 y; 46 female) were randomized and entered the treatment phase. Four patients withdrew their informed consent before the treatment phase because of factors unrelated to the study. Forty-five patients were randomized to receive the active treatment and 45 to the placebo group. There was no significant difference in sex, height, weight, smoker, alcohol intake, duration of IBS, and subtypes between the 2 groups (Table 1). Of these, 23 patients who were lost to follow-up, had adverse effects, took antidepressants, or had inadequately recorded symptom scores were excluded from efficacy analyses. Thirty-four patients completed the study in the treatment group and 33 patients in the placebo group.

Effect of *S. boulardii* on IBS-QOL

The percentage of changes in IBS-QOL scores before and after treatments were compared between the 2 treatment groups. Overall IBS-QOL improved in both groups compared with baseline; however, the *S. boulardii* group showed a significantly better improvement than the placebo group (15.4% vs 7.0%; $P < 0.05$; Table 2). All 8 domains (dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual, and relationships) of IBS-QOL were significantly improved in

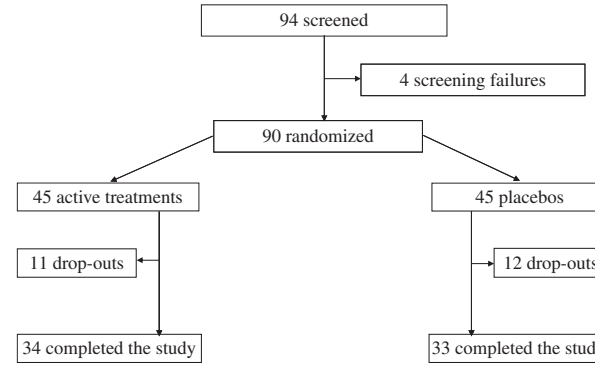

FIGURE 1. Schematic diagram of the study flow.

TABLE 1. Baseline Characteristics of Each Group

Characteristics	*S. boulardii* (N = 45)	Placebo (N = 45)	*P*
Age (y)	40.2 ± 13.1	40.6 ± 12.9	0.90
Sex (%)			0.82
Male	18 (51.4)	19 (48.7)	
Female	17 (41.6)	20 (51.3)	
Height (cm)	167.0 ± 8.8	164.8 ± 8.3	0.21
Body weight (kg)	64.9 ± 11.0	62.3 ± 14.2	0.40
Smoker	7 (20.0)	8 (20.5)	0.96
Alcohol intake	18 (51.4)	17 (43.6)	0.50
Duration of IBS (months)	81.1 ± 67.3	74.9 ± 95.9	0.90
Subtypes of IBS (%)			0.97
IBS-D	25 (71.4)	28 (71.8)	
IBS-M	10 (28.6)	11 (28.2)	

Data are shown as mean ± SD and numbers with percentages in parentheses.

IBS indicates irritable bowel syndrome; IBS-D, diarrhea-predominant IBS; IBS-M, Mixed-type IBS.

the *S. boulardii* group, but only dysphoria and health worry improved in the placebo group ($P < 0.05$; Table 2).

Effect of *S. boulardii* on Symptoms and Bowel Movement

Both groups showed improvement in the mean values of 10 symptoms over the treatment period (24.6% in *S. boulardii* and 20.4% in placebo; $P < 0.01$; Table 3). Of these 10 symptoms, abdominal discomfort, mucus in stool, and passage of gas were significantly improved in the *S. boulardii* group, whereas the placebo group showed improvement in loose/watery stool, sense of incomplete evacuation, and passage of gas ($P < 0.05$; Table 3). However, the percentage of changes in total mean scores and subscores were similar in the 2 groups (Table 3). Daily bowel movements were similar in the 2 groups and not changed significantly after treatment. Those were 1.8 ± 1.4 and 1.6 ± 0.8 before and after *S. boulardii* treatment, respectively, and 1.9 ± 1.2 and 1.4 ± 0.7 before and after placebo, respectively. Similarly, Bristol stool scale values were 4.9 ± 1.0 and 4.9 ± 1.2 before and after *S. boulardii* treatment, respectively, and 4.8 ± 1.2 and 4.2 ± 1.2 before and after placebo, respectively.

Adverse Events

No adverse events were reported in *S. boulardii* group (n = 39), but 1 patient in the placebo group (n = 43) withdrew due to worsening abdominal pain and flatulence.

DISCUSSION

IBS results from a multi-factorial pathophysiology that involves intestinal infection, immune activation, abnormal gastrointestinal motility, abnormal colonic fermentation, visceral hypersensitivity, increased intestinal permeability, autonomic nerve abnormality, psychosocial factors, specific gene abnormality, and intestinal bacterial overgrowth.[1,7,10,12,25–27] Current treatment of IBS, such as fiber, antidepressants, serotonin antagonists, and antispasmodics, focus on alleviating symptoms but are often unsatisfactory.[1] Probiotics can modulate the intraluminal milieu and inhibit inflammation to potentially treat IBS. However, the effects of probiotics in patients with IBS are still controversial, and a limited number of randomized controlled trials have been performed to validate the efficacy of probiotics for IBS.[22]

We, therefore, evaluated the effects of *S. boulardii* on QOL and symptoms in patients with IBS-D or IBS-M. Probiotic treatment improved overall QOL more than placebo. Not all IBS symptoms can originate in the bowel,[28] including psychological problems that affect relationships and social interactions, making QOL an important measure in patients with IBS[29,30] that determines when to initiate treatment.[31] Mental QOL includes sexuality, mood, and anxiety.[32] We used the Korean IBS-QOL questionnaire, a translation of the IBS-QOL questionnaire developed by Patrick et al[23] in Korean,[24] that contains 34 questions in 8 domains and has high reliability and internal validity. Body image and food avoidance are physical QOL components, whereas dysphoria, interference with activity, health worry, social reaction, sexuality, and relationships are mental QOL components. Probiotic treatment improved all QOL domains, whereas placebo only improved dysphoria and health worry.

The effects of both treatments were not different on secondary variables of individual symptoms and bowel

TABLE 2. IBS-QOL Mean Scores and Percentage of Changes Calculated by Scores Before and After 4 wk of Treatment

	QOL Mean Scores ± SD and Change Rates (%)						
	Baseline		After 4 wk		Change Rates (%)		
Domains of IBS-QOL	*S. boulardii*	Placebo	*S. boulardii*	Placebo	*S. boulardii*	Placebo	*P*
Dysphoria	68.0 ± 14.4	70.1 ± 23.2	79.3 ± 13.7	78.0 ± 18.7	19.5 ± 23.1	20.7 ± 36.8	0.87
Interference with activity	67.4 ± 18.9	74.2 ± 19.6	77.8 ± 17.8	76.0 ± 20.7	19.1 ± 23.2	4.2 ± 16.0	< 0.01
Body image	78.0 ± 17.6	77.1 ± 17.0	84.5 ± 16.4	79.9 ± 17.3	10.3 ± 22.3	6.4 ± 22.1	0.50
Health worry	65.6 ± 12.2	77.0 ± 15.3	79.4 ± 8.6	83.0 ± 9.7	24.8 ± 26.2	12.1 ± 27.3	0.07
Food avoidance	60.9 ± 22.6	58.6 ± 19.1	69.5 ± 22.2	65.8 ± 19.4	24.2 ± 46.4	23.1 ± 66.7	0.94
Social reaction	74.1 ± 17.5	81.1 ± 16.9	83.8 ± 15.1	82.6 ± 17.3	18.8 ± 33.7	3.0 ± 15.2	0.02
Sexual	86.6 ± 21.0	85.0 ± 20.9	92.9 ± 17.8	86.9 ± 18.9	10.9 ± 27.8	5.3 ± 21.8	0.39
Relationships	79.2 ± 13.7	80.0 ± 16.8	86.8 ± 13.3	83.6 ± 17.8	11.4 ± 19.7	6.7 ± 24.6	0.42
Overall	70.9 ± 12.8	74.8 ± 15.7	80.8 ± 12.3	79.0 ± 15.3	15.4 ± 16.4	7.0 ± 13.5	0.03

Change rate (%) = (Week 4 score − Week 0 score)/Week 0 score × 100.

Data are shown as mean ± SD.

IBS indicates irritable bowel syndrome; QOL, quality of life.

TABLE 3. Percentage of Changes of Likert Scores Calculated by Scores Before and After 4 wk of Treatment

	Likert Mean Scores ± SD and Change Rates (%)						
	Baseline		After 4 wk		Change Rates (%)		
Symptoms	*S. boulardii*	Placebo	*S. boulardii*	Placebo	*S. boulardii*	Placebo	*P*
Abdominal pain	1.6 ± 0.9	1.5 ± 1.2	1.3 ± 1.1	1.2 ± 0.9	−13.9 ± 72.1	−27.8 ± 127.9	0.13
Abdominal discomfort	2.2 ± 1.2	2.1 ± 1.2	1.3 ± 1.2	1.5 ± 1.1	−37.2 ± 46.1	−16.6 ± 73.6	0.19
Hard/lumpy stool	0.8 ± 0.6	1.2 ± 0.8	0.9 ± 1.1	1.1 ± 1.1	29.9 ± 207.9	14.6 ± 130.9	0.77
Loose/watery stool	2.4 ± 1.6	2.7 ± 1.4	1.9 ± 1.6	1.4 ± 1.2	−36.0 ± 98.7	−32.6 ± 68.1	0.15
Straining	1.6 ± 1.1	2.0 ± 1.3	1.1 ± 1.0	1.5 ± 1.3	−57.3 ± 317.7	−9.3 ± 80.2	0.28
Urgency	2.4 ± 1.6	2.1 ± 1.5	1.6 ± 1.3	1.3 ± 1.4	−20.9 ± 78.8	−26.8 ± 72.1	0.77
Sense of incomplete evacuation	2.3 ± 1.5	2.5 ± 1.6	1.4 ± 1.1	1.6 ± 1.3	−5.6 ± 159.4	−34.4 ± 50.9	0.19
Mucus in stool	0.9 ± 0.9	1.2 ± 1.0	0.3 ± 0.4	0.6 ± 0.9	−64.5 ± 53.0	−67.2 ± 46.9	0.89
Bloating	2.7 ± 1.4	3.0 ± 1.6	1.7 ± 1.3	2.2 ± 1.4	−21.1 ± 76.6	−13.8 ± 77.2	0.72
Passage of gas	2.7 ± 1.5	2.9 ± 1.5	1.7 ± 1.4	2.1 ± 1.4	−27.6 ± 53.7	−22.2 ± 54.9	0.69
Total	1.7 ± 0.8	1.8 ± 0.9	1.2 ± 0.8	1.3 ± 0.8	−24.6 ± 39.2	−20.4 ± 37.4	0.66

Change rate (%) = (Week 4 score − Week 0 score)/Week 0 score × 100.
Data are shown as mean ± SD.

habits. *S. boulardii* may have a greater effect on the small intestine than the colon, and therefore, be unable to improve colon-related symptoms. Alternatively, *S. boulardii* might improve overall QOL through systemic effects, such as inhibition of proinflammatory cytokines, which probably modulate the activity of the nervous system, or increases in tryptophan, rather than local effects, such as inhibition of mucosal inflammation, abnormal fermentation, or augmentation of mucosal barrier function.[33–35] Patients with fructose malabsorption show unusual bacterial profiles because of abnormal fermentation, leading to lower plasma tryptophan levels and subsequent depression.[36–39] *Bifidobacteria infantis* attenuates the production of proinflammatory cytokines and increased plasma levels of tryptophan in animals.[33] Probiotics also inhibit the release of adrenocorticotropic hormone and corticosterone,[40] and provoke behavioral alterations by releasing soluble factors.[41,42] Finally, dosing could have been sufficient to improve patient QOL, but inadequate to improve individual symptoms.

B. infantis significantly alleviated abdominal pain/discomfort, bloating/distension, and bowel movement difficulty compared with placebo.[34] In another study of 86 patients with IBS, probiotics improved the severity of IBS symptoms and QOL.[43] However, a fermented milk containing 3 probiotic bacteria was not effective on QOL and on symptoms in patients with IBS.[44] Our results may differ from these studies due to differences in probiotic strains or doses, racial differences, or different food habits of the study populations.

S. boulardii yeast has various advantages: it survives passage through the gastrointestinal tract, its temperature optimum is 37°C in vitro and in vivo, it inhibits the growth of microbial pathogens, and it has no severe adverse effects.[45] The clinical effect of *S. boulardii* has been proven in antibiotic-associated diarrhea, *Clostridium difficile* infection, traveller's diarrhea, acute diarrhea in children, tube-feeding-associated diarrhea, AIDS-related diarrhea, and inflammatory bowel diseases.[45–47] This probiotics work by: (1) anti-inflammatory effect; *S. boulardii* produced factors to neutralize bacterial toxins,[48] and inhibited the infiltration of T helper type 1 cells in the inflamed colon and the production of proinflammatory cytokines in IBS animal models.[49] (2) Immunoprotective effect in the gastrointestinal tract; oral administration of *S. boulardii* in rats stimulated intestinal secretion of IgA and expression of polymeric immunoglobulin receptor in intestinal glandular cells.[50] (3) Secretory effect on intestinal mucus; *S. boulardii* increased secretion and activity of the brush border enzyme.[51] Further studies are needed to elucidate the mechanism of action in patients with IBS.

Our short trial may have limited the ability to detect changes in individual symptoms, and we did not measure *S. boulardii* levels in the colon with microbial culture or DNA analysis. Finally, we only used 1 dose of *S. boulardii,* therefore, do not know the optimal dosing paradigm.

In conclusion, *S. boulardii* (Bioflor, Kuhnil) improved IBS-QOL, the primary endpoint, better than placebo in patients with IBS-D or IBS-M. Although it may be difficult to expect *S. boulardii* to improve specific symptoms prominently, overall satisfaction and QOL can be improved. Future studies to determine optimal dose, treatment duration, and mechanism of action of *S. boulardii* are needed.

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