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Original Research Article

Evaluation of efficacy and safety of Bacillus coagulans SNZ 1969 supplementation for irritable bowel syndrome: a randomized, double-blind, placebo-controlled study

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ABSTRACT

Background: Probiotic potential (efficacy and safety) of Bacillus coagulans SNZ 1969 has been studied in patients with constipation-predominant irritable bowel syndrome (IBS-C) and-diarrhea predominant IBS (IBS-D).
Methods: This randomized, double-blind, two-arm, placebo-controlled parallel study randomized 92 patients (1:1) to receive either 500 million CFU of Bacillus coagulans SNZ 1969 (treatment group) or placebo (placebo group) twice daily for 60 days under two subtypes of IBS, IBS-D (n=46) and IBS-C (n=46). Primary outcomes were changes in IBS symptom severity noted using the gastrointestinal symptom rating scale-IBS version (GSRS-IBS) on days 30, 60, and 75, and the number of treatment responders defined by subject's global assessment (SGA) of relief ≤3 and ≤2 at days 30 and 60, respectively. We also assessed patient's quality of life.
Results: The GSRS-IBS scores reduced from day 30 through 75 in both IBS groups treated with Bacillus coagulans SNZ1969 compared to placebo ($p<0.05$). Higher GSRS-IBS score was noted in patients with IBS-C in the treatment group (22.45±2.7) than the placebo group (3.55±3.02; $p<0.0001$), and this trend was similar in IBS-D patients ($p<0.0001$). Most patients (90%) with IBS-C and all with IBS-D responded to Bacillus coagulans SNZ 1969 compared to no responders with placebo ($p<0.0001$). The SF-8 scores significantly reduced in patients receiving Bacillus coagulans SNZ 1969 than placebo for both IBS subtypes. One adverse event unrelated to the study treatments was reported in IBS-D group.
Conclusions: Bacillus coagulans SNZ 1969 is safe, effective in alleviating IBS-associated clinical symptoms, and improves quality of life.

Keywords: Bacillus coagulans, Gastrointestinal symptom rating scale, Functional gastrointestinal disorder, Lactic acid-producing bacteria, Probiotics, SF-8 health survey, IBS-C, IBS-D, SNZ 1969

INTRODUCTION

Irritable bowel syndrome (IBS) is one of the most common functional bowel disorders in which recurrent abdominal pain is associated with defecation or change in bowel habits. Disordered bowel habits are typically present (i.e., constipation, diarrhea, or a mix of constipation and diarrhea) along with symptoms of abdominal bloating/distension. Symptom onset usually occurs at least 6 months before diagnosis and symptoms are present for 3 months and are currently diagnosed according to the new Rome IV criteria. IBS is classified into four subtypes: IBS with predominant constipation (IBS-C), IBS with predominant diarrhea (IBS-D), mixed bowel habits (IBS-M), or un-subtyped IBS.[1] The global prevalence of IBS is

reportedly 11% in heterogeneous population with a higher female gender predilection.[2-4] It interferes with the daily life of patients and reduces health-related quality of life (QoL) leading to a significant economic healthcare burden. Genetic background, environmental factors, positive family history, and psychological factors are involved in the pathogenesis of IBS.[5,6]

Complex multifactorial pathogenesis and heterogeneity in IBS presentation make treatment challenging. Although it is not completely elucidated, the proposed mechanisms of pathogenesis that leads to the development of IBS include altered gut microbiota, disturbance in the regulation of the gut brain axis, GI motility dysfunctions, chronic low grade mucosal inflammation visceral hypersensitivity, and psychosocial factors.[7] Since there is no effective cure for IBS, the treatment focuses on alleviating the particular symptoms. Pharmacologic and psychologic approaches such as tricyclic antidepressants, SSRIs, anti-spasmodic agents, lubiprostone, linaclotide, and 5HT3 antagonists such as ramosetron and alosetron are considered therapeutic options in IBS patients. However, due to lack of favorable efficacy, associated adverse events with pharmacologic treatments and non-addressal of critical pathogenic factor of altered microbial composition, emergence of use of probiotic supplementation is a promising and safer alternative therapeutic option. Recent clinical evidence emphasizes importance and the role of altering gut microbiota in IBS pathogenesis, and this has introduced newer treatment approaches like probiotics. Given the fact that all available treatment options only provide symptom relief only for a certain subset of patients, probiotics may be an effective alternative.[8]

Probiotics are live microorganisms, when administered in adequate amounts, can provide health benefits to the host. Evidence demonstrates that the mechanism of action of probiotics in IBS is diverse and heterogeneous, and can be summarized as 1) modulation of the gut microbiota through the competitive exclusion of pathogens (luminal pH, competition for nutritional sources, and production of bacteriocins, SCFAs, and biosurfactants) which prevent the proliferation of pathogens and inhibit their adhesion to the gut epithelia; 2) enhancing the gut barrier function through increased mucus secretion, improvement in the integrity of tight junctions between intestinal epithelial cells and the production of antimicrobial peptides by epithelial cells; 3) stimulation of secretory IgA production and resultant improved gut immunity; 4) probiotics also strengthen the immune system by differentiating T-regulatory cells and upregulating anti-inflammatory cytokines and growth factors, and 5) supporting the regulation of endocrine and neurological functions enhance the gut-brain communication.[9] However, all the aforementioned mechanisms of action depending on the strain of probiotics, delivery of a sufficient amount of active cells (CFUs), and duration of therapy.

Different strains of Bacillus coagulans have been identified as beneficial in IBS treatment.[10-16] Sanzyme Biologics has developed an oral probiotic, which contains a lactic acid-producing bacteria, Bacillus coagulans SNZ 1969. Previous studies demonstrated that the combination of Bacillus coagulans SNZ 1969, Bacillus clausii (SNZ 1971), and Bacillus subtilis (SNZ 1972) relieved GI discomfort symptoms such as burping/belching, bloating, and sour taste.[17,18] In India, whichever probiotics are studied for IBS, are either studied on patients with either IBS-D or IBS-C but not in both. Gastrointestinal symptoms of patients with IBS may switch from one type to other. Thus, in this randomized, double-blind placebo-controlled study, we determined the efficacy and safety of Bacillus coagulans SNZ 1969 in patients with IBS-D and IBS-C.

METHODS

Study design

This randomized, double-blind, two-arm, placebo-controlled parallel study was conducted at the medical gastroenterology department, Apollo hospitals, Jubilee Hills, Hyderabad, between June 2021 to April 2022. All patients were randomized (1:1) to receive either the Bacillus coagulans SNZ 1969 (treatment group) or the placebo (placebo group).

This study was conducted after receiving approval from the institutional ethics committee (Institutional ethics committee-Biomedical research; Apollo hospitals, Hyderabad. This study was conducted following pertinent requirements of the declaration of Helsinki (Brazil, October 2013), good clinical practices for clinical research in India 2005, new drugs and clinical trials rules 2019, ICH E6 (R2), guidance on good clinical practice, and with ICMR's national ethical guidelines for biomedical and health research involving human participants-2017. This study was registered with the clinical trial registry of India (registration no. CTRI/2021/04/032513) [Registered on: 05/04/2021]-trial registered prospectively.

Study population

Patients of either sex (age: 18-50 years) were included in the study if they fulfilled the inclusion criteria 1) Patients with symptoms of functional IBS as per the Rome IV diagnostic criteria for the past 3 months with the symptom onset at least 6 months prior diagnosis, 2) GSRS-IBS pain score (question 1 and 2) between seven and twelve, 3) willingness to follow protocol requirements including response to study questionnaires and completing subject diaries, 4) willingness to provide written informed consent, 5) agreed to not use any other (including vitamins and minerals) medication except study treatment and rescue medicine during the study period, 6) agreed to not use any yogurt during the study period, 7) laboratory investigations within the normal ranges or clinically insignificant if outside the normal range, and 8) did not take antibiotics/other products which had GI tract as their primary site of action until 1 month prior study initiation.

However, patients were excluded if they: 1) were diagnosed with functional dyspepsia/other functional GI disorder, 2) had clinically significant medical history/finding or an ongoing medical/psychiatric condition, which in the opinion of the Investigator, could jeopardize their safety, impact validity of study results or interfere with study completion, 3) unhealthy subject based on medical history, physical examinations and laboratory investigations that include complete blood count, C-reactive protein estimation and liver function tests, or patients with abnormal laboratory findings (baseline history, physical examination, vital signs, complete blood count, liver function test [LFT], C-reactive protein [CRP]), 4) had a history of significant alcoholism/product abuse in the past one year, 5) were smokers or consumed tobacco products, 6) had a history of malignancy/other serious disease, 7) had contraindication to blood sampling, 8) participated in a clinical study 75 days prior study initiation, 9) were pregnant or lactating, 10) used laxatives daily within one to three month of screening, and 11) used any antibiotics (e.g. neomycin, rifaximin) within 1 month of screening.

Considering a 40% reduction in symptom severity between the two treatment groups, as per published literature, and 80% power at a 5% level of statistical significance, a sample size of 60 subjects (IBS-D: n=30, and IBS-C: n=30) was calculated for this study, which was further increased to 80 subjects (40 subjects in each group) based on an assumption of 30% dropout rate.[19]

Study products and procedure

Before initiating study treatments, all subjects underwent baseline clinical evaluation including physical examination and baseline laboratory investigations, performed by the Principal Investigator and his team.

The study enrolled 46 patients who were diagnosed with IBS-D and 46 patients who were diagnosed with IBS-C. These patients were then randomly allocated (1:1) to treatment group (IBS-D: n=23; IBS-C: n=23) and placebo group (IBS-D: n=23; IBS-C: n=23) (Figures 1 A and B). The principal investigator assigned participants to interventions in a random and double-blind fashion. Patients in the treatment group received one capsule containing 500 million colony forming units (CFU) of Bacillus coagulans SNZ 1969 twice daily-morning and night along with breakfast and dinner, respectively. Similarly, patients in the placebo group received placebo capsules that comprised maltodextrin which had a similar color and shape to the Bacillus coagulans SNZ 1969 capsule. Patients were given the study medications on an outpatient basis and the dosing period was for 60 days. They were instructed to maintain their daily food intake in their respective subject diaries. Further, they were also asked not to take yogurt/any medication (other than study treatments and rescue medications prescribed by the investigators) during the study period. Rescue medications were prescribed as per hospital standards if the patient demanded alternate therapy due to worsening/persistent symptoms.

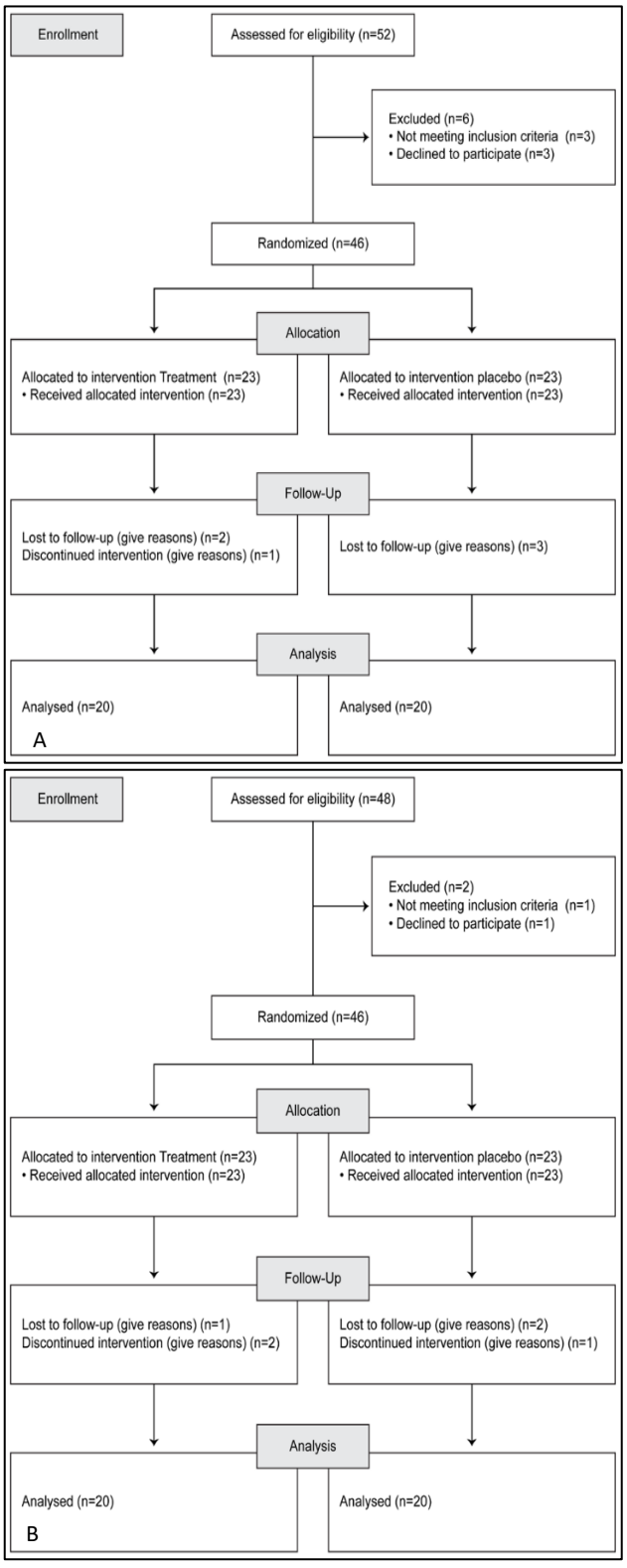

Figure 1 (A and B): Patient disposition for IBS-D and IBS-C subtypes.

All patients were clinically evaluated on days 30 and 60 after initiating the study treatments for reassessing IBS

symptoms and safety evaluation (or in case of any adverse events [AE]). Treatment compliance at each visit was assessed by examining the returned packet/bottle.

The randomization schedule was generated by an independent statistician using a computer-generated randomization list. Investigators, patients, and research associates were blinded to the study treatments.

Study endpoints

The primary endpoints of the study were as follows: Change in severity of IBS symptoms severity using the gastrointestinal symptom rating scale-IBS version (GSRS-IBS) at 30, 60, and 75 days compared with baseline GSRS-IBS is a validated questionnaire that was used to evaluate IBS symptoms experienced by patients after one week of treatment initiation.[20] It contains a series of 12 items that evaluate the pain syndrome (Q 1 and 2), bloating syndrome (Q 3, 4, and 13), constipation syndrome (Q 5 and 8), diarrhea syndrome (Q 6, 7, 9, and 10), and satiety (Q 11 and 12). Questionnaire used to the assess treatment effects.[21]

Patients were required to rate their symptoms at baseline and days 30, 60, and 75 after initiation of symptoms on a 7-point Likert scale (1=no discomfort at all, 2=minor discomfort, 3=mild discomfort, 4=moderate discomfort, 5=moderately severe discomfort, 6=severe discomfort, and 7=very severe discomfort).

The number of responders to treatment as defined by subject's global assessment (SGA) of relief on days 30 and 60.

The SGA of relief evaluated overall wellbeing, symptoms of abdominal discomfort, pain, and altered bowel habit to identify responders to therapy.[22] Symptom severity was rated on a 5-point scale ranging from complete relief from symptoms (score 1) to worsening of symptoms (score 5). Responders were defined as patients with scores $\leq$3 at day 30 and score $\leq$2 on day 60 after initiating study treatment.

The secondary endpoint of the study was the overall health and well-being of subjects measured by the SF-8 health survey questionnaire on days 30, 60, and 75 after treatment initiation compared to baseline.

The SF-8 health survey (4-week recall) is used to measure the subject's QoL.[23] It contains physical and mental health summary measures, and the questionnaire was slightly amended to make it more applicable for IBS (in questions #2 and #3 "physical health" was replaced with "gut health", and in question #4 "bodily pain" replaced with "abdominal pain"). Thus, 8 domains of amended version measured general health, physical functioning, the role of gut health, abdominal pain, vitality, social functioning, mental health, and the role of emotional problems in all the subjects. Each item was scored on the five- or seven-point scales.

The SF-8 questionnaire was administered to each patient at baseline (before treatment initiation) and on days 30, 60, and 75 after treatment initiation.

Safety

The safety and acceptability of study treatments were assessed by the occurrence of new AEs on days 30, 60, and 75 of treatment.

Statistical analysis

Statistical analysis was performed based on the per-protocol analysis. Continuous variables are summarized as Mean and standard deviation (SD) whereas categorical variables are expressed as frequencies (%). Differences between the two treatment groups for GSRS-IBS and SF-8 scores were measured using an unpaired t-test or Mann-Whitney test, depending on the normality distribution of data. The Chi-square test or Fischer's exact test was applied to compare the number of responders in both treatment groups. A $p<0.05$ was considered statistically significant. Statistical analysis was performed using SAS version 9.4 or higher (SAS Institute Inc., USA).

RESULTS

Baseline characteristics

Of the total of 100 IBS patients (IBS-D: n=52 and IBS-C: n=48) screened for eligibility, 92 were randomized to receive the treatment. Of randomized patients, 40 patients in each subgroup completed the study (Figure 1 A and B). The mean age of patients with constipation-predominant irritable bowel syndrome in the treatment and placebo groups was 42.65±5.05 and 42.1±4.66 years, respectively, and the corresponding values for patients with IBS-D were 44.75±4.28 and 40.95±5.28 years in both groups, respectively (Table 1).

Change in the GSRS-IBS score

Patients with IBS-C who were treated with the probiotic Bacillus coagulans SNZ 1969, showed a significant reduction in the GSRS-IBS score beginning from day 30 through day 75 compared to placebo (Table 2). The mean change from baseline to day 75 in the GSRS-IBS score was 22.45±2.7 in the treatment group compared to 3.55±3.02 in placebo group ($p<0.0001$). Approximate % reduction in the GSRS-IBS score was greater in the treatment group (39.78%) compared to the placebo group (2.42%). Consistent reductions in the GSRS-IBS score also seen in patients with IBS-D from baseline (62.5±3.9) to day 75 (34.45±3.53) (mean change: 28.05±4.43, $p<0.0001$) after treatment with Bacillus coagulans SNZ 1969.

Responders

Of all, 90% of patients with constipation-predominant irritable bowel syndrome responded to the treatment as

defined by SGA ≤3 at day 30 and SGA ≤2 at day 60 compared to no responders in the placebo group, p<0.0001 (Figure 2 A). Similarly, all patients with IBS-D (100%) responded to the Bacillus coagulans SNZ 1969 treatment compared to no responders in the placebo group, p<0.0001 (Figure 2 B). The change in SGA score in the treatment group and placebo group is summarized in supplementary Table 1.

Health-related QoL

Treatment with probiotic Bacillus coagulans SNZ 1969 showed improvements in health-related quality of life as was evident by a decrease in the SF-8 scores at all follow-up time points. Compared to placebo, there was a significant reduction in the mean SF-8 score at day 75 in patients with constipation-predominant irritable bowel syndrome who were treated with probiotic Bacillus coagulans SNZ 1969 (2.50±1.88 vs. 13.60±1.76, p<0.0001). A consistent decrease was seen in the SF-8 scores of patients from the IBS-D group and those treated with probiotic Bacillus coagulans SNZ 1969 compared to patients who received a placebo (1.15±1.14 vs. 18.85±1.98, p<0.0001) (Table 3) thus improving the health-related quality of life of patients in the treatment group.

There was one adverse event (nausea and vomiting) reported in one patient who received Bacillus coagulans SNZ 1969 in the diarrhea predominant irritable bowel syndrome group.

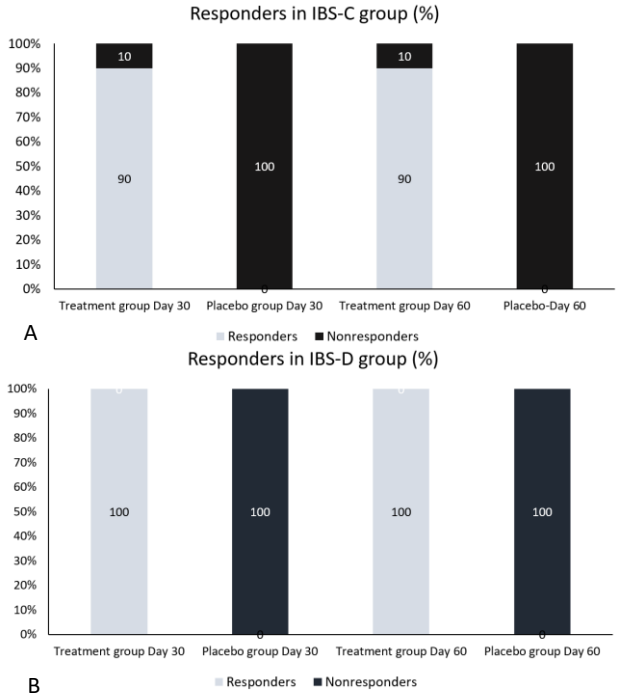

Figure 2 (A and B): Responders as per the SGA score, responders in the IBS-C group, and IBS-D group.

Table 1: Demographic characteristics of the study population. (n=20).

Variables	IBS-C		IBS-D	
	Treatment group	Placebo group	Treatment group	Placebo group
Age (years), mean ± SD	42.65±5.05	42.1±4.66	44.75±4.28	40.95±5.28
Sex, N (%)				
Male	14 (70.00)	15 (75.00)	15 (75.00)	12 (60.00)
Female	6 (30.00)	5 (25.00)	5 (25.00)	8 (40.00)

Table 2: Change in the GSRS-IBS score, (n=20).

Variables	IBS-C		IBS-D	
	Treatment group	Placebo group	Treatment group	Placebo group
Baseline	56.35±3.18	56.1±3.24	62.5±3.9	62.25±4.19
30 days	46.45±3.05	55.05±3.25	55.45±5.61	62.8±3.93
Change from baseline	9.90±1.71	4.15±3.28	7.05±2.93	2.45±2.04
P value	<0.0001		<0.0001	
% change from baseline	-17.56±2.92	-1.48±9.18	-11.42±5.01	1.03±5.29
60 days	37.2±2.84	55.1±2.94	37.1±3.88	62.7±4.01
Change from baseline	19.15±2.68	3.6±2.95	25.4±4.15	3.85±2.03
P value	<0.0001		<0.0001	
% change from baseline	-33.95±4.10	-1.46±7.92	-40.58±5.77	0.98±7.09
75 days	33.9±2.36	54.55±2.42	34.45±3.53	62.35±3.6
Change from baseline	22.45±2.7	3.55±3.02	28.05±4.43	2.60±1.76
P value	<0.0001		<0.0001	
% change from baseline	-39.78±3.63	-2.42±7.58	-44.78±5.74	0.33±5.20

Table 3: Change in the SF-8 scores, (n=20).

Variables	IBS-C		IBS-D	
	Treatment group	Placebo group	Treatment group	Placebo group
Baseline	32±1.86	31.9±1.8	31.6±1.88	31.65±1.6
30 days	26.25±0.79	30.75±2.51	21.55±1.85	31.65±1.93
Change from baseline	5.75±1.65	2.85±2.64	10.05±2.01	1.6±1.27
P value	<0.0001		<0.0001	
% change from baseline	-17.76±4.31	-3.09±11.72	-31.72±5.55	0.78±6.48
60 days	18.55±1.19	31.2±2.46	13.9±1.92	32±1.59
Change from baseline	13.45±1.65	2.40±1.67	17.70±2.23	1.05±1.05
P value	<0.0001		<0.0001	
% change from baseline	-41.94±3.70	-1.94±9.08	-55.97±5.81	-1.21±4.68
75 days	18.4±1.1	30.9±1.83	12.75±2	31.7±1.92
Change from baseline	13.60±1.76	2.50±1.88	18.85±1.98	1.15±1.14
P value	<0.0001		<0.0001	
% change from baseline	-42.39±3.87	-2.72±9.33	-59.68±5.65	0.23±5.03

DISCUSSION

IBS is a common disorder of the gut-brain interaction and affects approximately 1 in 10 individuals globally.[24] It adversely affects the patient's QoL.[25] We evaluated the efficacy and safety of treatment with probiotic capsules containing Bacillus coagulans SNZ 1969 in patients with constipation-predominant IBS (IBS-C) and diarrhea-predominant IBS (IBS-D). Our results showed that compared to placebo, 60 days of supplementation with Bacillus coagulans SNZ 1969 improved functional symptoms and QoL which was apparent by improvements in GSRS-IBS score, SGA score, and SF-8 score respectively.

We assessed the severity of symptoms using the GSRS-IBS scale as it has several advantages compared to other self-rating scales such as IBS-SSS and PROMIS GI symptom scales.[20] In this study, patients who were treated with probiotic Bacillus coagulans SNZ-1969 for 60 days demonstrated improvement in the overall GSRS-IBS scale which was statistically significant compared to placebo starting from day 30 through day 75 after probiotic administration.

Probiotics are emerging as effective adjunctive and alternative therapeutic agents for treating IBS. Several meta-analyses have confirmed the efficacy of different probiotics in improving functional symptoms and QoL in patients with IBS.[26-29] These studies have also shown improvement in depression and anxiety among patients with IBS.[30] However, there are contradicting results for the optimal dose and duration of probiotic treatment.[31-32] A network meta-analysis by Zhang et al showed that among all available probiotics, Bacillus coagulans had the highest potential to be the optimal probiotic in terms of improvement in IBS symptom relief rate, global symptoms, abdominal pain, bloating, and straining scores.[29] To exert their beneficial effects, probiotics must survive gastric and bile acids before reaching the intestinal tract but the conventional forms of probiotics (mainly, lactobacilli-type) are non-spore forming and mostly get inactivated by bile and low gastric pH. However, Bacillus coagulans strains are spore-forming bacteria that are resistant to heat and can survive in acidic gastrointestinal conditions to reach the intestine to proliferate within the host.[26] Bacillus coagulans also offer other therapeutic benefits, mainly by changing the gut microbiome and related metabolic modulation that result in better digestion and immune homeostasis.[13]

Various Bacillus coagulans strains have been reported to provide probiotic benefits in patients with IBS.[10,12-14,16] However, these studies were conducted on diarrhea-predominant IBS or mixed-type of IBS. However, in our study, evaluated efficacy in 2 separate patient subgroups with IBS-C and IBS-D. Our results showed that treatment with Bacillus coagulans SNZ 1969 significantly improved the GSRS-IBS, GSA, and SF-8 scores in both types of IBS.

There was no study of drug-related adverse events or serious adverse events noted during trial, which suggests that twice daily treatment with capsules containing 500 million CFU of Bacillus coagulans, SNZ 1969 was well-tolerated and safe for use in patients with IBS.

There were some limitations in this study. Firstly, patient compliance was only checked quantitatively using subject diaries from visit to vist schedules and no metrics were maintained. Secondly, while all patients were advised to maintain their usual dietary practices throughout the study, and this was monitored formally at client visits, no nutritional assessments were undertaken to confirm dietary adherence. Lastly, routine colonoscopy was not performed in these patients to rule out the presence of microscopic colitis (MC), as is the case for almost all studies in this therapeutic setting of IBS.

CONCLUSION

In conclusion, the probiotic Bacillus coagulans SNZ 1969 with a dose of 500 million CFU twice a day was well-

tolerated and showed significant alleviation of IBS-associated clinical symptoms compared to placebo and improved the QoL of IBS patients, and could be used as a therapeutic supplement in IBS management. Future clinical trials are still required that can confirm the effectiveness of probiotics on specific and major IBS symptoms and patient QoL.

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Conflict of interest: None declared
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Appendix

Supplementary table

Table 1: Changes in the subject's global assessment of relief scores, (n=20).

Variables	IBS-C		IBS-D	
	Treatment group	**Placebo group**	**Treatment group**	**Placebo group**
Baseline	4.75±0.44	4.75±0.44	4.7±0.47	4.6±0.5
30 days	2.75±0.64	4.55±0.51	2.85±0.37	4.75±0.44
Change from baseline	2.00±0.46	0.60±0.50	1.85±0.37	0.25±0.44
% change from baseline	-42.50±10.20	-3.00±17.04	-39.25±7.12	4.00±11.65
60 days	1.75±0.64	4.55±0.51	1.85±0.37	4.6±0.68
Change from baseline	3.00±0.46	0.50±0.51	2.85±0.37	0.60±0.60
% change from baseline	-63.75±11.34	-3.25±15.33	-60.75±7.12	1.25±19.39
75 days	1.75±0.64	4.6±0.5	1.7±0.47	4.55±0.69
Change from baseline	3.00±0.46	0.45±0.51	3.00±0.56	0.45±0.60
% change from baseline	-63.75±11.34	-2.25±14.82	-63.75±9.98	-0.25±17.05