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Single-blind follow-up study on the effectiveness of a symbiotic preparation in irritable bowel syndrome

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OBJECTIVE: Experimental and clinical studies have shown that a novel symbiotic (known as SCM-III) exerts a beneficial effect on gut translocation and local and systemic inflammatory and microbial metabolic parameters. The present investigation was a preliminary trial on the effectiveness of SCM-III for irritable bowel syndrome (IBS).

METHODS: Sixty-eight consecutive adult patients with IBS who were free from lactose malabsorption, abdominal surgery, overt psychiatric disorders and ongoing psychotropic drug therapy or ethanol abuse were studied prospectively and divided into 2 groups that were comparable for age, gender, body size, education and pattern of presenting symptoms. The 2 groups were blindly given for 12 weeks either SCM-III 10 mL t.i.d or the same dosage of heat-inactivated symbiotic.

RESULTS: Treatment with SCM-III was 'effective' or 'very effective' in more than 80% of the patients ($P < 0.01$ vs baseline values and control). Less than 5% reported 'not effective' as the final evaluation compared with over 40% of patients in the control group. After 6 weeks of treatment, a significant improvement of pain and bloating was reported in the treatment group compared with control and baseline values. There was also a benefit for bowel habits, mostly for patients with constipation or alternating bowel habits. No overt clinical or biochemical adverse side-effects were recorded.

CONCLUSION: Compared with baseline values and the control group, SCM-III resulted in a significant increase in lactobacilla, eubacteria and bifidobacteria, which suggests that some selected IBS patients could benefit substantially from symbiotics, but the treatment may need to be given on a cyclic schedule because of the temporary modification of the fecal flora.

KEY WORDS: irritable bowel syndrome, SCM-III, symbiotic.

INTRODUCTION

Irritable bowel syndrome (IBS) is a multifaceted, but frequent syndrome that represents approximately 50% of patients consulting a gastroenterologist. The clinical picture is characterized by abdominal pain and abnormal bowel functions with diarrhea and/or alternate constipation, bloating and distension lasting for at least 3 months. It is ubiquitous, estimated to affect up to 20% of individuals in Western populations, and seems to be more common in females.[1,2] Although a number of sensory-motor abnormalities have been suggested as the mechanism during the past two decades,[3–5] and some recent drugs have been reported as beneficial,[6–9] the overall understanding, and hence the established treatment of this condition, still remains rather elusive. Given the complex interplay between the gut ecosystem and gastrointestinal function, manipulation of the gut flora through viable bacteria administration has been proposed as a further rational

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therapeutic option.[10–12] Probiotics are defined as viable microorganisms that when ingested exert beneficial effects in the prevention and treatment of specific pathologic conditions such antibiotic-associated diarrhea, traveller's diarrhea and some viral enteritis.[13–17] Although any such study suffers from intrinsic methodological limitations, there are a few well-planned investigations that show a significant beneficial effect on IBS symptoms after probiotic administration.[18,19] A further possibility in microflora management procedures is the use of symbiotics in which the live microbial species are used in combination with specific substrates (prebiotics) for growth and improved survival.[20] We have recently shown in experimental and clinical studies that a novel symbiotic, known as SCM-III (Microflorana-F, Named, Lesmo, Italy), had a significantly beneficial effect on gut translocation and local and systemic inflammatory and microbial metabolic parameters.[21–24] Thus the present investigation was a preliminary trial on the usefulness of that symbiotic in an IBS population.

MATERIALS AND METHODS

Study population

A total of 68 consecutive adult subjects with IBS (20 males, 48 females; mean age, 46 years, range: 36–65 years) were studied prospectively and divided into 2 equal groups that were comparable for age, gender, body size, education and pattern of presenting symptoms. Overt concurrent or past psychiatric disease or frequent use (≥3 times/week) of any psychotropic drugs was regarded as an exclusion criterion. The diagnosis of IBS was made using the ROME II diagnostic criteria.[25] Using the current inclusion criteria, the specificity of the IBS diagnosis was retrospectively and blindly evaluated by a third party and found to be 94%. Only patients with a significant score of a definitive diagnosis were included. The mean number of years since first diagnosis was 6.1 years with bowel habit alternating between diarrhea and constipation, according to standardized criteria.[1] All patients had previously undergone a number of treatments (antispasmodic drugs, exclusion diet, intestinal antibiotics, herbal remedies etc.) without significant and lasting benefit. Because of either overlapping[26] or subjectively reported lactose malabsorption,[27,28] which has similar symptoms, all patients were initially screened by lactose H_2-breath test and found to be negative. None of the patients had concomitant disease and all had normal hematology, biochemistry and urinalysis, together with a normal colonoscopy or barium enema (for patients over 50 years old), which had been done within the past 18 months. None had a prior history of abdominal surgery, which was an exclusion criterion. Female subjects were excluded if they were pregnant or were breast feeding and were studied during the first phase of the menstrual cycle or while taking estrogen/progesterone contraceptive medication. All patients were symptomatic at the time of the study, and lower abdominal discomfort or pain together with significant abnormal bowel habit were the main reasons for referral to the physician. No patient was on any therapy for IBS at the time of evaluation and entry into the study. There was no past or ongoing history of heavy alcohol, drug or cigarette abuse. Eleven patients (6 males, 5 females) were mild smokers (<10 cigarettes/day) and 35 were mild coffee or tea drinkers (<3 cups/day).

Study design

The previously matched-groups were blindly given for 12 weeks either SCM-III 10 mL t.i.d. (composition for 100 mL: *Lactobacillus acidophilus* 1.25×10^6, *L. helveticus* 1.3×10^9, *bifidobacterium* 4.95×10^9 in a vitamin- and phytoextracts-enriched medium) or the same dosage of a heat-inactivated symbiotic preparation. Evaluation of efficacy, tolerance and compliance were assessed before and after the placebo treatment period and after 3, 6 and 12 weeks of treatment. Patients were instructed to rate the defined parameters on diary cards. At each visit, the overall clinical status (OCS) was arbitrarily scored: 1, no symptoms; 2, light discomfort; 3, mild discomfort; 4, severe discomfort; 5, incapacitating abdominal complaint. The overall clinical improvement (OCI) was assessed at each visit using a three-point scale: 1, improvement; 2, unchanged; 3, worsening. At the end of treatment period, the treatment was evaluated by both the patient and the physician: −1, worsening; 0, not effective; +1, slightly effective; +2, effective; +3, very effective. The main parameters of efficacy were the patient's and physician's evaluations and the OCS and OCI after 6 and 12 weeks. Specific symptoms such as abdominal pain and the presence/absence of bloating and their intensity were also assessed at baseline and at 3, 6 and 12 weeks: 0, no symptoms; 1, awareness of symptoms without discomfort; 2, discomfort not interfering with normal daily activities; 3, interfering with daily activities; 4, incapacitating, unable to perform normal daily activities. The number of defecations/day and stool consistency were assessed and pooled together as 'bowel habits', which was scored as for the other specific symptoms. Tolerance was evaluated on the basis of clinical history and examination and routine biochemical tests. A specific form regarding adverse effects was provided to patients and physicians.

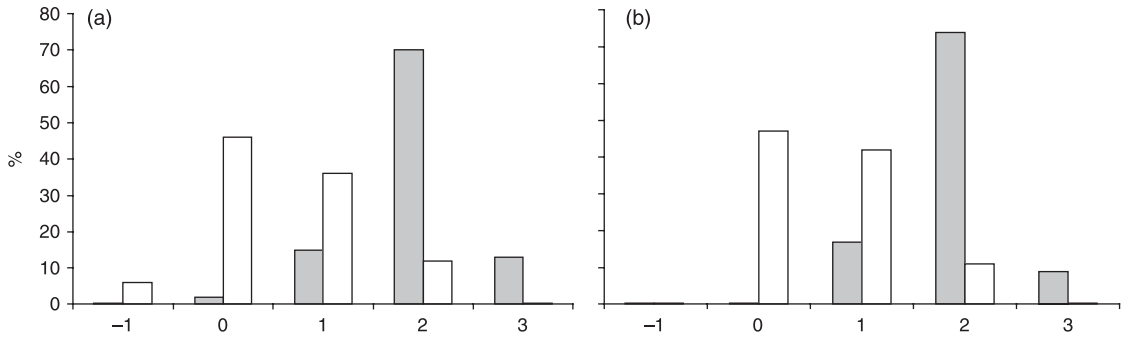

Figure 1. Overall clinical assessment at 12 weeks. (a) Patients' assessment; (b) physicians' assessment.

Assessment of intestinal bacterial flora

At the entry and end of the study, determination of the bacterial flora in fecal samples was carried out within 12 h of collection as reported by Mitsuoka *et al.*[29] Briefly, 9 mL of a diluent was added to 1 g of fecal sample, the mixture was vigorously shaken and 10-fold serial dilutions of the suspension were prepared. Each dilution was set in aliquots of 0.05 mL onto agar plates of media, which were appropriate for the target organisms. The organisms were identified and counted after incubation for 48 h at 35°C for aerobes and for 72 h at 35°C for anaerobes in an anaerobic tube. Bacterial identification was based on the morphology of the colonies, microscopic examination of Gram-stained slides, tests for growth under aerobic conditions and appropriate biochemical tests. Peptone yeast extract solution was used to examine the bifidus factors derived from non-carbon sources. The bacterial cells were sedimented at 3000*g* for 10 min, washed three times with 5 mL of sterile physiological saline (0.85% NaCl, 0.1% L-cysteine-HCl, 0.1% sodium thioglycolate) and finally suspended in 5 mL of reduced physiological saline. The number of organisms per gram of feces was calculated, the lower limit of detection being 2×10^2 colony forming units/g of each isolate.

The fecal flora study was also carried out in 10 healthy asymptomatic subjects, matched with the patient population for age, gender, dietary habits and lack of overt food intolerance.

Statistical analysis

All statistical tests were two-sided, at a 5% level of significance. Descriptive statistics were calculated for the demographic characteristics of the patients at selection. The scores of efficacy, OCS, OCI, and the intensity and frequency of the symptoms were evaluated at 3 and 6 weeks and compared with baseline values and the controls by the Mann-Whitney-Wilcoxon rank test.

RESULTS

After 6 and 12 weeks of treatment, the overall efficacy of the treatment was assessed by the patient and the final 12-week evaluation results, expressed in percentage, are shown in Figure 1. Treatment with SCM-III was regarded as 'effective' or 'very effective' in more than 80% of the patients ($P < 0.01$ vs baseline values and control). No worsening was reported as a final assessment at the end of the study period and less than 5% reported 'not effective' as the final evaluation as compared with more than 40% of patients in the control group. Similar results were recorded for the physicians assessments.

On further analysis, two-thirds of the patients still reporting mild discomfort had a predominant pain presentation, but had normalized their bowel habits (data not shown). Figure 2 shows the patients assessments of the intensity of abdominal pain; after 6 weeks, a significant improvement was reported in the group treated with SCM-III as compared with control and baseline values ($P < 0.05$). Similar results were

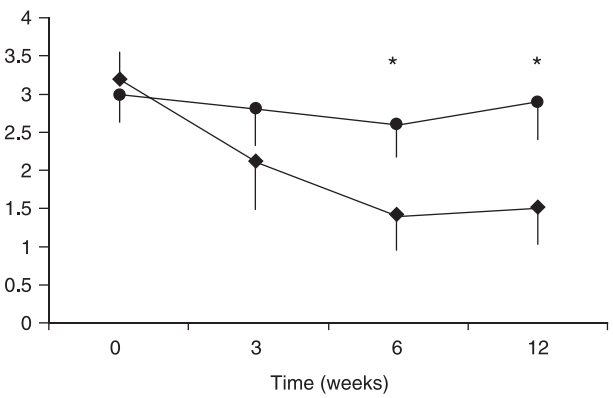

Figure 2. Time-course assessment of abdominal pain intensity: effect of symbiotic (mean ± SD). (◆) SCM-III, (●) control.

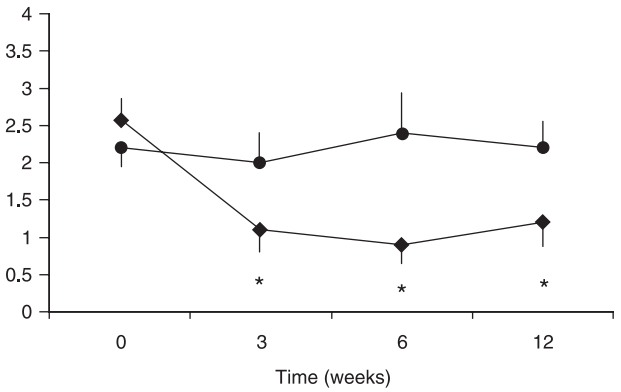

Figure 3. Time-course assessment of bowel habits: effect of symbiotic (mean ± SD). (◆) SCM-III, (●) control.

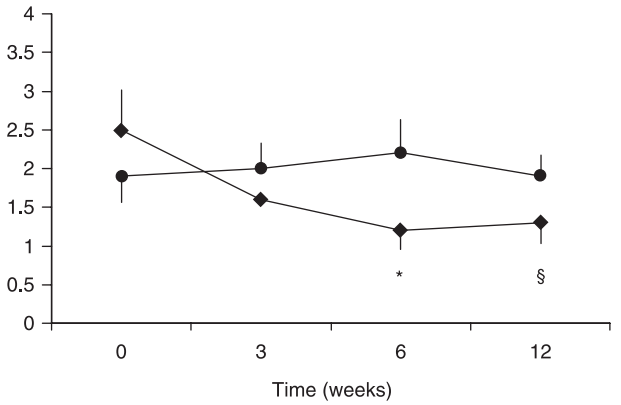

Figure 4. Time-course assessment of abdominal bloating intensity: effect of symbiotic (mean ± SD). (◆) SCM-III, (●) control.

obtained for bowel habits for which an earlier benefit at 3 weeks was observed in the treatment group (Figure 3). As far as the bloating sensation was concerned, the symbiotic treatment brought about a significant improvement when compared to baseline values and the controls at the 6-week observation (Figure 4). However, at the 12-week time point that significance was maintained only in comparison with the baseline assessment within the treatment group, but was overlapping the results in the placebo-treated group.

No overt clinical or biochemical adverse side-effects were recorded, although a few patients presenting with diarrhea-like symptoms reported a transient early worsening of this complaint. However, that symptom subsided within 4–5 days and did not affect their final reported effectiveness. Approximately 12% complained about the palatability of the symbiotic.

The microbiological study (Table 1) showed that, as compared with baseline values and to the group treated with heat-inactivated symbiotic, the live compound resulted in a significant increase ($P < 0.05$) in the lactobacilla, eubacteria and bifidobacteria composition of the fecal microbiota. The fecal flora composition in IBS patients was comparable that of healthy subjects.

DISCUSSION

Irritable bowel syndrome is a common, chronic functional disorder worldwide with a multifaceted etiology, affecting 10–20% of all individuals at any one time. Psychological factors, altered motility[30] and sensation disorders of the intestine because of lowered visceral perception thresholds and a disordered perception are variably associated with this condition.[31] Several expert commissions have tried to establish the correct assessment of IBS, and more recently, revised Rome diagnostic criteria have been proposed.[25] The present study population adhered strictly to these criteria. However, the condition remains elusive for satisfactory clinical management and still poses a considerable challenge to the clinician who has often to rely on a symptom-based empirical approach.[32,33] Although it has long been accepted that gut bacteria play a role in host pathogenesis, current opinion is that certain microflora components can exert beneficial effects on gastrointestinal immunity and resistance to

Table 1. Fecal flora assessment in irritable bowel sydrome after live SCM-III or heat-inactivated preparation

	Bacterial species (log no./g wet feces)		
	Healthy control	Heat-inactivated symbiotic	SCM-III
Total aerobes	8.15 ± 0.31	(8.21 ± 0.20) 8.14 ± 0.24	(8.19 ± 0.18) 8.26 ± 0.27
Total anaerobes	9.80 ± 0.24	(9.89 ± 0.19) 10.03 ± 0.13	(9.43 ± 0.19) 11.26 ± 0.16*
Lactobacillus	8.10 ± 0.21	(8.17 ± 0.16) 8. 20 ± 0.17	(8.08 ± 0.18) 8.53 ± 0.11*
Eubacterium	8.31 ± 0.21	(8.27 ± 0.27) 8.48 ± 0.15	(8.36 ± 0.15) 9.23 ± 0.21*
Bifidobacterium	9.46 ± 0.26	(9.36 ± 0.19) 9.19 ± 0.24	(9.59 ± 0.23) 12.33 ± 0.32*

Pretreatment values are shown in brackets.
*$P < 0.05$ vs pretreatment values.

gastroenteritis, blood lipids, lactose tolerance and carcinogenesis.[34,35] Thus, modulating the gut flora for improved health is gaining an increasing popularity for the management of either acute or chronic gut disorders and some studies have suggested that probiotics are as effective as antispasmodic drugs in alleviating IBS.[36] When considering the often reported unresponsiveness or the unpredictability of the duration of a beneficial response to any treatment, it is of interest to note in the present study that using SCM-III achieved a significant general improvement that lasted for the whole 12-week period, as judged by the patients and clinicians. Patients reported a time-course improvement of pain that was statistically significant from the 6-week observation point onward, although none of them had complete relief. A further analysis showed that patients enrolled with the main presentation of 'pain-presenting' IBS symptoms constituted more than two-third of the cases with a final score of 'not effective'. A similar pattern was observed for 'bloating' for which there was significantly improvement with SCM-III only after the 6th week and at the end of the study period the related score was not distinguishable from the group treated with inactive symbiotic. On the other hand, an early significant improvement was recorded in bowel habits for those presenting with constipation and they were the ones who mostly received benefit from the treatment. Overall, patients presenting with constipation or alternating bowel movements as the main disturbing symptom represented most of the cases who scored the final result of the treatment as 'very effective'/'effective'. Although there are few reports suggesting that patients suffering from IBS might have an abnormal fecal flora composition with a decrease in the coliforms, lactobacilli and bifidobacteria,[37] our study did not confirm such findings. Nonetheless, as compared with heat-inactivated symbiotic, SCM-III significantly manipulated the gut ecosystem by increasing the lactobacilli, eubacteria and bifidobacteria populations, which is in agreement with the recent finding that probiotics can significantly modify the enzymatic activity of the fecal flora.[38] Although we did not perform any enzymatic analyses in the present study, we have very recently shown that this particular symbiotic was able to beneficially modify the gut flora and its metabolic activity in patients with liver cirrhosis,[24] which might also explain its efficacy in lowering ammonia, endotoxin and benzodiazepines-like substances in this complex clinical setting.[39] Similarly, molecular biological analysis was not performed to confirm the survival and persistence of the symbiotic, as would be expected for an effective compound.[40] However, preliminary in-house studies using pulsed-field gel electrophoresis have shown the viability in the gut of this symbiotic preparation (unpubl. data).

Overall, taking into account the limitation of any study tackling the issue of treating a heterogeneous IBS population, it would appear that SCM-III exerts a significant beneficial effect on IBS, especially for those patients presenting with constipation and alternating bowel habits. As compared with other similar investigations[41] our study was carried out with a stricter clinical selection, which excluded concomitant lactose intolerance, and for a longer period. We conclude that some selected IBS patients could receive substantial benefit from symbiotics, but the treatment may need to be tentatively given on a cyclic-administration schedule because of the temporary modification of the fecal flora.[42,43]

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