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ORIGINAL PAPER

Failure of Synbiotic 2000 to Prevent Postoperative Recurrence of Crohn's Disease

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Abstract Complications of Crohn's disease (CD) lead to surgery in about 70–90% of patients. The majority of patients suffer from relapse of the disease. Colonic bacteria are essential to the development of CD. Therefore, a rationale exists in trying to prevent relapse by manipulation of gut microflora. This is feasible by treatment with probiotics or antibiotics. Synbiotic 2000 is a cocktail containing 4 probiotic species and 4 prebiotics. It is rational to pursue that it could be effective in preventing postoperative disease. We sought to check weather treatment with Synbiotic 2000 could prevent postoperative recurrence in patients with CD. This was a prospective multicenter, randomized study. Patients were randomized to active treatment or placebo in a 2:1 ratio. Follow-up consisted of endoscopic, clinical, and laboratory parameters. Thirty patients were enrolled. No differences were found between the 2 treatment groups regarding gender, age at diagnosis, age at surgery, weight, smoking status, type of disease, length of the resected segment, or medical treatment prior to surgery. No difference in either endoscopic or clinical relapse rate was found between patients treated with once daily dose of Synbiotic 2000 or placebo. In our small study, Synbiotic 2000 had no effect on postoperative recurrence of patients with CD. Larger studies in patients with the inflammatory type of CD undergoing surgery, using higher doses of probiotics cocktail might prove effective.

Keywords Crohn's disease · Probiotics · Prebiotics · Synbiotics · Postoperative recurrence

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Crohn's disease (CD) is an inflammatory disease of the gastrointestinal tract. Complications of CD lead to surgery in about 70–90% of the patients over the years [1]. The majority of these patients will suffer from relapse of the disease [2, 3]. Multiple strategies exist to try and prevent this from happening. There is uniformity in studies regarding cessation of smoking as an important factor in preventing recurrence. 5-ASA treatment may lower the postsurgical endoscopic recurrence rate in CD [4], and 6-MP may be efficient, especially in high-risk patients with multiple previous resections [5].

Colonic bacteria are essential for CD to develop and the colonic flora of patients suffering from CD is different

than healthy individuals [6]. Therefore, a rationale exists in trying to treat the disease by manipulation of gut microflora. This may be feasible by either treating the patient with probiotics or antibiotics. Further stimulation of probiotics growth and effect can be achieved by using prebiotics.

Antibiotics such as metronidazole or ornidazole have been shown to reduce relapse rate of postsurgical CD [7, 8]. Probiotic regimens have been shown to be effective mainly in preventing postsurgical recurrence of pouchitis in patients suffering from ulcerative colitis after proctocolectomy. This was shown very elegantly using the probiotic regimen VSL#3 [9, 10]. Two studies addressed the issue of probiotic treatment to prevent postoperative recurrence for CD. *Lactobacillus* GG was proven ineffective in preventing CD recurrence after resection [11], as was *L. johnsonii* LA1, which did not prevent endoscopic recurrence of Crohn's disease in 98 patients [12]. Thus, 1 of the most effective probiotics for treating inflammatory bowel disease (IBD) so far is VSL#3 which contains multiple probiotic bacteria [9, 10, 13–16].

Prebiotics, for example, fructo-oligosaccharides, which are nondigestible polymers of fructose, were found to stimulate the growth of intestinal probiotic bacteria such as bifidobacteria [17]. Lindsay *et al*. [18] treated 10 patients with active CD with 15 g of fructo-oligosaccharides for 3 weeks and demonstrated a significant reduction in the Harvey Bradshaw index, and significant increase in fecal bifidobacteria concentration. The percentage of interleukin-10–positive dendritic cells increased, as did the percentage of dendritic cells expressing toll-like receptor (TLR)-2 and TLR-4. The conclusion from this small, open-label trial was that this therapeutic strategy may decrease CD activity [18].

A *synbiotic* is a regimen where probiotics are combined with prebiotics. Using a combination made it logical that Synbiotic 2000 containing 4 probiotic bacteria and 4 prebiotics, could prevent postsurgical relapse in patients suffering from CD. Thus, the aim of our study was to determine weather Synbiotic 2000 prevents postsurgical recurrence of CD.

Methods

This was a prospective, multicenter study enrolling patients from 4 medical centers in Israel. Patients suffering from CD, undergoing resection in 1 of the medical centers affiliated with the study and who were eligible to take part according to their physician participated in the study. All patients provided informed consent. The local Helsinki committees approved the study.

The study was conducted as a randomized, double-blind, placebo-controlled study. Patients were randomized to active treatment or placebo in a 2:1 ratio. Active treatment consisted of Synbiotic 2000, which contains a mixture of prebiotics and probiotics, including 4 lactic acid bacteria and 4 fermentable fibers. The 4 lactic acid bacteria are 10^{10} *Pediacoccus pentoseceus,* 10^{10} *L. raffinolactis,* 10^{10} *L. paracasei* susp paracasei 19, and 10^{10} *L. plantarum* 2362; the 4 fermentable fibers are 2.5 g β-glucans, 2.5 g inulin, 2.5 g pectin, and 2.5 g resistant starch. Treatment began as soon as patients resumed oral intake after surgery. Follow-up visits were scheduled at 0, 1, 2 and 3 months and every 3 months thereafter till 24 months postsurgery. Follow-up consisted of endoscopic, clinical, and laboratory parameters. Endoscopy was preformed at 3 months postsurgery and at completion of the study (24 months) or withdrawal using the Rutgreets scoring system [1]. Clinical parameters included weight, number of bowel movements, and abdominal pain (on 0–4 scale). Laboratory parameters included complete blood count, electrolytes, urea, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein, albumin, erythrocyte sedimentation rate (ESR), and C-reactive protein. Statistical analysis was preformed using the SPSS with χ^2 or Fischer's exact test and Student's *t*-test or Mann–Whitney for comparison between the 2 groups. Paired *t*-test was used to compare 2 time points.

Results

We enrolled 30 patients. We initially intended to enroll 60 patients, but encountered problems in achieving this because patients and physicians were reluctant to participate in a study where there was a placebo arm. Because the interim analysis did not reveal a benefit toward the active treatment, a decision was made to cease enrollment after 30 patients. No differences were found between the 2 treatment groups regarding gender, age at diagnosis, age at surgery, weight, smoking status, type of disease, length of resected segment, or medical treatment prior to surgery (Table 1). Twenty-three men and 7 women were enrolled. They were 26.7 ± 10.2 years of age at diagnosis and 35.7 ± 12.2 years of age at surgery, and weighed 64.4 ± 17.5 kg at enrollment. At the time of surgery, 30% were current smokers, 3 (10%) had inflammatory type of disease, and the extent of ileal resection was 34.4 ± 20 cm. Twenty-eight of 30 patients were treated with a 5-ASA compound prior to surgery; 29 of 30 patients were treated with immunosuppressants prior to surgery. All patients were treated with at least 1 course of steroids. In our limited study, no difference in either endoscopic or clinical relapse rate was found between patients treated with once daily dose of Synbiotic 2000 or placebo (Table 1). Significant improvement appeared in the following parameters after 3 months of follow-up: weight gain, decline in ESR,

Table 1 Baseline Patient Data

	Placebo	Active Treatment	Statistics
Male/female	8:2	15:5	NS
Age at diagnosis	25.4 ± 7.6	27.4 ± 11.5	NS
Age at surgery	34.7 ± 9.9	36.1 ± 13.0	NS
Weight	64.4 ± 17.1	64.5 ± 13.2	NS
Current smokers	2/10 (20%)	8/20 (40%)	NS
Type of disease			
Noninflammatory	9	18	NS
Inflammatory	1	2	NS
Patients who had previous operations	2 (20%)	4 (20%)	NS
Length resected part (cm)	32.9 ± 21.7	34.9 ± 18.8	NS

normalization of hemoglobin level, and rise in albumin. Further improvement occurred after 1 year postsurgery, but proved statistically significant only for the rise in hemoglobin and albumin. No significant difference was found between the 2 groups relating to improvement of the above mentioned indices (Table 2). Kidney function tests and electrolytes were normal throughout the study in all patients. One patient in the active treatment group had mild AST and ALT elevation (2.5 times the normal value), but normalization occurred within 3 months after enrollment. Twenty-one patients underwent endoscopy at 3 months, 15 from the active treatment group and 6 from the placebo group. Rutgreets score was 0.8 ± 1 in the placebo group and 0.6 ± 0.8 in the treatment group (P = NS). Eight patients underwent endoscopy at 24 months, 7 from the active treatment group and 1 from the placebo group. No difference was found in the percentage of patients completing the study between the groups or in the reasons for withdrawal (Table 3). Nine patients completed the study, 7 from the active treatment group and 2 from the placebo. Altogether, no differences were observed between the 2 groups in the clinical, laboratory and endoscopic outcome.

Discussion

In the present study, a single dose of the synbiotic 2000 regiment was found ineffective in preventing postsurgical recurrence of CD. *Probiotics* includes a large spectrum of bacteria having different effects on different diseases. Two

Table 2 Follow-Up of Patients Treated With Either Synbiotic 2000 or Placebo

	Placebo				Active Treatment				
	0	3	12	24	0	3	12	24	
[Weight] Months mean ± SD	64 ± 17	67 ± 17	76 ± 17	76 ± 30	65 ± 13	68 ± 13	72 ± 14	71 ± 12	NS
Patients (n)	10	8	4	2	20	18	7	8	
Erythrocyte sedimentation rate ($N < 8$ mm/h)	31	25	0	10	49	21	13	21	
Patients (n)	8	5	0	1	12	13	4	5	
C-reactive protein ($N < 5$ mg/L)	1.9	2.2	2.7	0	5.7	4.3	5.3	2.0	NS
Patients (n)	5	6	3	0	7	16	4	4	
Hemoglobin ($14 < N < 18$ g/dL)	11.6	12.7	14.2	13.4	11.6	12.7	13.3	12.9	NS
Patients (n)	10	8	4	2	20	19	9	8	
Albumin ($3.5 < N < 5.5$ g/dL)	3.2	4.0	4.2	4.4	3.3	4.0	4.1	4.0	NS
Patients (n)	10	8	2	2	19	19	8	7	
Abdominal pain[a]	<1	<1	<1	<1	<1	<1	<1	<1	NS
Patients (n)	9	7	3	3	20	19	8	7	
Bowel movements (n)	3	3	2	2	~4	~4	~4	~3	NS
Patients (n)	9	8	4	2	18	19	10	9	
Rutgreets score at 3 mos	0.8	1	0.6	1.7	NS				
Patients (n)	6	1	15	7					
Crohn's disease activity index at 3 mos	102	72	54	110	NS				
Patients (n)	7	1	15	3					

[a] Abdominal pain on a 0–3 score scale.

Table 3 Reasons for Withdrawal

	Placebo	Active	All Groups
Self-withdrawal	3	5	8
Exacerbation	2	5	7
Arthritis and arthralgia	1	1	2
Pregnancy	1	1	2
Fistula	0	1	1
Postoperative complications	1	0	1
Completed study (24 mo)	2	7	9
Total	10	20	30

major differences appear to be responsible for this phenomenon: (1) different clinical settings (e.g., maintenance of remission versus induction of remission and inflammatory versus other manifestations); and (2) different compositions and amounts of probiotics. Theoretically, there are many reasons to assume that probiotics or even better synbiotics may have a role in the treatment of IBD including CD and in the prevention of postoperative relapse of CD. Knowledge of IBD etiology and the understanding of the mechanisms of action of pro and prebiotics lead to this conclusion [19], but the clinical efficacy in CD has thus far been unsuccessful, including the present study. This was true for single-strain probiotics or, in our study, a combination of 4 probiotics and 4 prebiotics. The only clinical setup in IBD in which probiotics prove consistently effective was in the prevention and treatment of pouchitis [9, 10].

On the whole there, is ≥ 1 explanation for the inefficacy of probiotics and synbiotics in CD in general, and specifically in this study. The number of patients may be too small; different disease state (e.g., maintenance versus active disease); postoperative versus no operation; different disease manifestation (e.g., inflammatory versus stricturing); different strains of bacteria; interaction between bacteria; insufficient dosage; or negative interactions between specific probiotics and prebiotics.

Different probiotics have different effects and the same probiotic might be effective in a certain clinical setting and totally ineffective in a different setting. Patient selection is also important. It is assumed that probiotics counteract the inflammatory process, so it is be logical to assume that patients with dominant inflammatory elements benefit most, whereas patients with stricturing or fistulizing disease are likely to benefit less. Probiotics may exert their effect by changing the flora and thus may be more effective in colonic disease.

This is a small cohort with only a small minority of the patients having the inflammatory type of disease, and this could be a crucial reason for the failure of treatment. Other reasons for the failure of synbiotic treatment in the present study might be the dose (1 sachet daily), the specific probiotic stains or some of them, the specific prebiotics or some of them, or, as mentioned, the specific combination of probiotics and prebiotics.

In summary, in our small study, Synbiotic 2000 had no effect on postoperative recurrence of patients with CD. Larger studies in patients with the inflammatory type of CD undergoing surgery, using higher doses of a probiotic cocktail, might prove effective.

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