



## Applied nutritional investigation

## Impact of the preoperative use of synbiotics in colorectal cancer patients: A prospective, randomized, double-blind, placebo-controlled study



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## ABSTRACT

**Objectives:** Gastrointestinal microflora is involved in the development and regulation of the immune response. Non-pathogenic bacteria are important to prevent the development and subsequent invasion of enteropathogenic bacteria. Surgical trauma and intestinal preparation can disrupt the intestinal microbiota balance. Modulating the microbiota in the preoperative period in patients with colorectal cancer may have an effect on the occurrence of postoperative complications. The aim of this study was to assess the effect of preoperative synbiotic administration in patients with colorectal cancer subjected to colorectal resection.

**Methods:** This was a prospective, randomized, double-blind, placebo-controlled study of 73 patients with colorectal cancer. Eight days before surgery, patients were randomized to receive either synbiotics (Simbioflora, Fermoquímica, São Paulo, Brazil) or placebo (maltodextrin). The envelopes were identical and labeled A or B. All patients underwent nutritional assessment and measurements of C-reactive protein (CRP), interleukin (IL)-6, serum albumin, and transferrin. Patients were given a diluted envelope in 100 mL of water twice daily for 7 d. The occurrence of infectious or non-infectious complications, time of antibiotic use, duration of hospitalization, and occurrence of deaths were recorded for 30 d postoperatively.

**Results:** Mean age, demographic data, and tumor staging were similar between the groups at baseline. After 7 d of synbiotic intake, there were significant reductions in IL-6 levels ( $163.2 \pm 19.5$  versus  $138.8 \pm 12.5$ ,  $P < 0.001$ ) and CRP ( $10 \pm 5.2$  versus  $7.17 \pm 3.2$ ,  $P < 0.001$ ), whereas the control group did not present significant changes in IL-6 levels ( $154.2 \pm 18.3$  versus  $160.9 \pm 18.6$ , NS) or CRP ( $10.6 \pm 6.18$  versus  $10.4 \pm 6.1$ , NS). Serum albumin and transferrin did not show significant changes. Postoperative infectious complications occurred in 2.8% of patients in the synbiotic group and in 18.9% of the control group ( $P = 0.02$ ). The mean antibiotic usage time was  $1.42 \pm 0.5$  d in the synbiotic group and  $3.74 \pm 4.3$  d in the control group ( $P < 0.001$ ). The mean hospital length of stay was  $3 \pm 1$  d in the synbiotic group and  $4 \pm 18$  in the control group ( $P < 0.001$ ). Three deaths were reported in the control group and none in the synbiotic group ( $P = 0.115$ ).

**Conclusions:** The use of synbiotics for 7 d preoperatively in patients with colorectal cancer attenuates the inflammatory state and is associated with reductions in morbidity, hospital length of stay, and use of antibiotics.

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## Introduction

Colorectal cancer (CRC) occurs equally in both sexes and, when localized, often is a curable disease. Surgical resection is the primary treatment, removing the affected portion of the intestine and regional lymph nodes [1,2]. However, colonic resection for malignancy is associated with significant postoperative morbidity,

reaching 25% to 30% of cases, and often associated with dehiscence of the anastomosis, abdominal infection, and fistula formation [2,3].

To reduce the risk for postoperative complications, several strategies were investigated, such as perioperative nutritional therapy, particularly with the administration of so-called immunomodulatory nutrients, reduction of the preoperative fasting period, and initiation of an oral diet early in the postoperative period, among other recommendations included in the Enhanced Recovery Pathways protocols [4–6].

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Some of the infectious complications that occur after colorectal surgery are attributed to the translocation of pathogens and toxins from the gut [7,8]. Bacterial translocation is associated with increased incidence of postoperative sepsis [7]. Disruption of the balance of the intestinal microbiota by invading microorganisms and their products, known as dysbiosis, can occur after surgical trauma, bowel preparation, and use of antibiotics in the perioperative period. The consequences of dysbiosis include inflammatory reaction, leading to the destruction of the intestinal barrier and subsequent bacterial translocation, which results in increased postoperative infectious complications [9].

Modulation of intestinal microbiota in the perioperative period is a therapeutic option to reduce the rate of postoperative complications [10]. It is possible to manipulate the composition of gut microflora by administering both prebiotics and probiotics, or their combination, known as synbiotics. These have been shown to be effective therapies to modulate the intestinal barrier [7].

Some recent studies have emphasized the important role of probiotics in gastrointestinal surgery [11]. Different types of microorganisms have been studied as regulators of the human intestinal flora with the function of reducing infections and increasing the cellular immunity, particularly by increasing the production of immunoglobulins, reduction of “killer” cell activity, and increase interleukin (IL) production, particularly IL-6 [12].

In general, the use of synbiotics in elective surgery in patients without risk factors is safe. However, care should be taken when using probiotics or synbiotics in immunosuppressed or critically ill patients as their use in such circumstances has been associated with infectious complications [8].

Recently, Liu et al. conducted a meta-analysis on the effects of probiotics on the intestinal mucosal barrier in patients with CRC. They evaluated the outcomes of 1242 patients and concluded that the administration of probiotics can effectively protect the intestinal mucosal physical and biological barriers in patients with CRC postsurgery [13].

Most studies in CRC surgery evaluated the perioperative administration of probiotics [12]. Because synbiotics are an association of one or more probiotics added to a fiber source, such fiber addition may confer additional advantages [9]. Also, the use of fiber stimulates the intestinal peristalsis. Thus, considering that postoperative infectious complications in CRC patients often are due to microorganisms derived from the bowel, the preoperative manipulation of the gut microbiota arises as an interesting alternative to prevent infectious complications after surgery. The aim of this study was to evaluate the effect of the preoperative administration of synbiotics on the inflammatory response, and in postoperative morbidity and mortality in patients with CRC.

## Materials and methods

This was a prospective, randomized, double-blind, placebo-controlled study that included patients with CRC who were candidates for colorectal resection. The research protocol was approved by the Ethics Committee in Research with Human Beings of the Erasto Gaertner Cancer Hospital in Curitiba, Brazil.

### Study design

The patients selected for research were new cases referred to the institution. Each patient had a diagnosis of CRC and the primary treatment proposed was surgery.

In some patients with CRC, chemotherapy or chemotherapy and radiotherapy is first choice, with surgery occurring after. However, to minimize the bias due to malnutrition, diarrhea, and a possible chance of intestinal flora induced by chemotherapy, radiotherapy, or a combination of the two, we only included patients who underwent surgery as first-line treatment. Unfortunately, it is not possible to determine how long these patients had cancer before diagnosis; however, the

time from diagnosis to surgery was 20 to 25 d. Exclusion criteria included the following:

- patients who were immunosuppressed
- patients with metastatic disease
- patients on enteral nutrition therapy
- presence of unresectable tumors
- presence of systemic infections requiring treatment with antibiotics in the previous 30 d
- pregnant or breastfeeding women
- patients who used prebiotics, probiotics, or synbiotics in the 3 mo before the intervention
- patients who were lost to follow-up

A randomizing sequence with two groups was generated by GraphPad statistical software (QuickCalcs, in La Jolla, CA, USA), allocating the patients in each group. Both the patients and the study investigators remained blinded until after the statistical analysis was completed.

Envelopes containing either synbiotic or placebo-containing bags that were identical and sealed and packed in boxes labeled A or B were provided to study participants. After determining which label should be delivered to the patient, the samples marked A and B were given to the principal investigator to give the same orientation and instruction to all patients. They were instructed to dilute the product in 100 ml of water and ingest orally twice a day for 7 d before the date of the surgical procedure, the last dose being defined the day before surgery.

The synbiotic used was Simbioflora (Farmoquímica, São Paulo, Brazil), a dietary supplement comprising 6 g of fructooligosaccharide, and the probiotics *Lactobacillus acidophilus* NCFM, *L. rhamnosus* HN001, *L. casei* LPC-37, and *Bifidobacterium lactis* HN019 in the concentration of 10<sup>9</sup>. The placebo was maltodextrin (obtained from cornstarch). It is a carbohydrate module that is not associated to either benefit or harm to the patient.

During the 7-d intervention, the principal investigator called each patient daily to make sure that he or she was using the product as instructed. During this intervention period, the patients completed a daily food log to quantify dietary fiber intake.

At the beginning of the intervention, all patients underwent a nutritional status assessment and the following biochemical tests were performed: C-reactive protein (CRP), IL-6, serum albumin, and transferrin, which were repeated the day before surgery and after 7 d of use of the synbiotic or maltodextrin.

Postoperative information collected included the surgical procedure performed, tumor staging, and the occurrence of infections or non-infectious complications, as well as hospital length of stay (LOS), antibiotic usage, bowel function, fiber intake, definitive diagnosis, and occurrence of death.

### Nutritional status

Anthropometric data were oriented at baseline. Based on height (in m) and weight (in kg), body mass index (BMI) was determined and classified according to age, with >70 y being considered elderly [14]. Percentage of weight loss (%WL) was calculated in relation to the current and usual body weight of the patient, with %WL >10% in 6 mo being considered severe [15].

### Analysis of biochemical data

Measurements of serum albumin, transferrin, CRP, and IL-6 were collected after a 12-h fast before the beginning of the administration of synbiotics or placebo.

Serum albumin and total lymphocyte counts were determined by routine laboratory methods. The reference values considered for the tests were previously defined [16]. CRP was determined by an immunonephelometric method, which is based on determining the motion of particles in solution (turbidity) formed by antigen-antibody complexes (CRP linked to the monoclonal antibody 77 anti-CRP; Siemens Dade Behring, Deerfield, IL, USA). IL-6 analysis was performed by quantitative enzyme immunoassay “sandwich” assay (ELISA; R & D, Minneapolis, MN, USA) as described by the manufacturer. Assays were performed in triplicate and the mean values were used.

All exams were collected 8 d before surgery and were repeated 1 d before surgery, after a 12-h fasting period. It was not possible to perform dosages the surgery because of cost issues.

### Analysis of fiber intake

The assessment of fiber intake was carried out by completing a 7-d food record [17]. The record was completed daily during the preoperative study period. Patients recorded information such as time of consumption and size of each portion.

A photo album with photos of food portions and utensils was used to assess total dietary fiber intake [18,19]. Portion sizes were converted to grams and milliliters according to the standardization of measures of the Table Referred to the Food Consumed in Brazil, the Household Budget Survey [19]. The analysis of the nutritional composition of foods and meals was conducted through a structured spreadsheet based on information about the composition of foods as recommended by the Nutritional Composition Table of Food Consumed in Brazil [19].

#### Postoperative complications, postoperative LOS, and antibiotic use

Data were collected from the electronic medical record of each patient, including the clinical course, postoperative bowel function, occurrence of postoperative infections and or non-infectious complications, length of antibiotic usage, and mortality in the period up to 30 d after the procedure [20]. Hospital LOS was calculated from the day of surgery to the time of hospital discharge.

#### Tumor staging

Tumor staging was based on the TNM classification of the seventh edition of the International Union Against Cancer, published in 2010 and translated into Portuguese in 2012 by the National Cancer Institute. The classification includes the degree of tumor invasion (T), the number of metastatic lymph nodes (N), and the presence of metastasis (M) [21].

#### Bowel preparation

On the day before surgery, all patients underwent colon preparation with an oral solution prepared with 20% mannitol diluted in 500 mL of water plus a rectal enema with 800 mL of 0.9% saline solution mixed with 200 mL of 50% glycerin. No oral antibiotic was used. The use of abdominal drains was determined intraoperatively by the surgeon, based on his or her experience.

All patients received prophylactic antibiotics for 24 h. The antimicrobial regimen was the combination of metronidazole (500 mg 8/8 h for 24 h) and ceftriaxona (2 g in a single dose) for all operations intravenously, beginning at anesthesia induction. Antibiotic therapy was maintained for >24 h by decision of the responsible surgeon, and the total length of antibiotics usage was calculated for each patient. Prophylactic low-molecular-weight heparin was used subcutaneously in all patients at anesthesia induction.

#### Sample size and statistical analysis

The sample size was obtained by sampling proportions. The sample size was defined in the number of 77 cases, randomly divided into two groups, based on an expected complication rate of 30% in the control group and an expected reduction of 20% in the study group, with 95% confidence interval (CI) and 8% error. Statistical analysis was performed with description of absolute frequencies of the results obtained. The data were classified into categorical variables. Student's *t* test was performed for IL-6 and CRP.

The  $\chi^2$  test was performed to associate categorical variables of group characteristics, nutritional status, and infectious and non-infectious complications. Statistical analyses were performed by the SPSS version 19.0 for Windows

(SPSS, Chicago, IL, USA). Statistical significance was set at  $P < 0.05$ , with a 95% CI.

## Results

During the intervention period, four patients were excluded because they did not take the product according to the recommendation (Fig. 1). Of the 77 enrolled, 4 did not comply with treatment after the study. The characteristics at inclusion of the study are shown in Table 1. There was no statistical difference between groups at baseline.

It was not possible to evaluate stage III because of the small number of patients in this stage, six in the synbiotic group and seven in the placebo group.

Baseline data showed homogeneity with respect to sex, age, and nutritional status between the two groups. The type of surgery and staging of the disease also were similar between groups.

In general, the synbiotics were well tolerated, with the most frequently reported side effect being flatulence ( $n = 4$ ; 11.1% and  $n = 3$ ; 8.1%, respectively;  $P = 0.34$ ).

In assessing the nutritional status by BMI and %WL, no significant difference was detected between the groups. Weight loss <10% in the previous 6 mo was reported by 80.6% and 81.1% of patients in the placebo and synbiotic groups, respectively ( $P > 0.05$ ).

Mean serum albumin was  $3.8 \pm 0.5$  for the synbiotic group and  $3.9 \pm 0.6$  for the control group. Twenty-nine patients (80.6%) in the synbiotic group and 28 in the placebo group (75.9%) had levels within the normal range ( $P > 0.05$ ), with mean being  $3.8 \pm 0.5$  for the synbiotic group and  $3.9 \pm 0.6$  for the control.

There were no differences in CRP and serum IL-6 levels between groups at baseline. However, after the intervention, there was a significant reduction in the levels of both IL-6 and CRP in the synbiotic group; whereas no change was observed in the control group, as shown in Figures 2 and 3.

Unfortunately, no correlation test was performed for CRP, IL-6, and albumin, but the values of these variables were equally distributed in both groups.

Regarding the occurrence of infectious and non-infectious complications, infectious complications were lower in the synbiotic group than in the control group (2.8 versus 18.9%,  $P = 0.02$ ). There were four cases of non-infectious complications (10.8%), and all

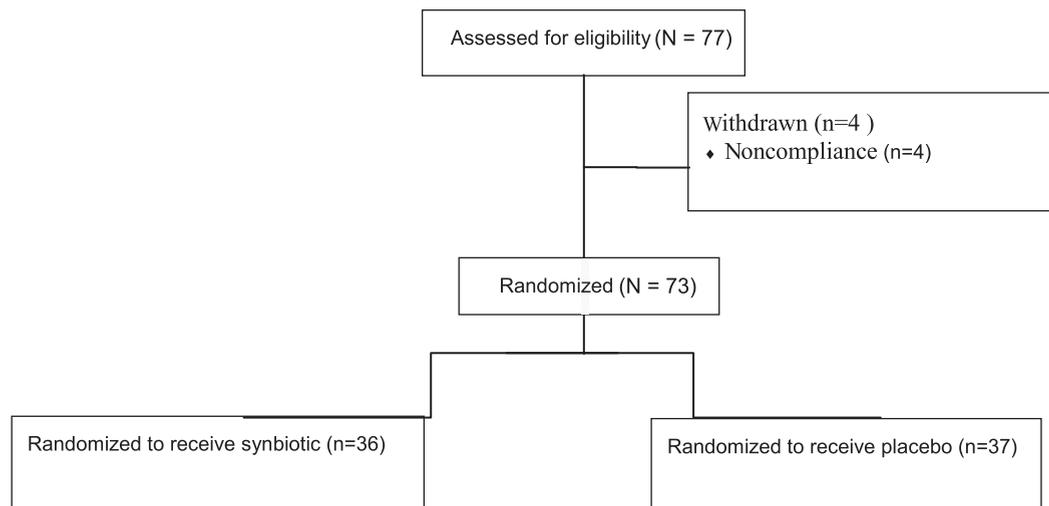


Fig. 1. Patient selection, treatment, and analysis.

**Table 1**  
Characteristics of the research participants

Variable	Synbiotic (n = 36)	Placebo (n = 37)	P-value
Mean age $\pm$ SD	60.9 $\pm$ 6.7	58.9 $\pm$ 6.3	0.207
Sex, male (%)	20 (55)	19 (51)	0.719
Calorie intake	1566 $\pm$ 18.6	1629 $\pm$ 24.1	0.42
BMI, kg/m <sup>2</sup> , mean $\pm$ SD	24.8 $\pm$ 3.2	24.9 $\pm$ 2.9	0.890
%WL (>10% 6 mo)	1.6 $\pm$ 3.1	0.8 $\pm$ 3.1	0.273
Serum albumin (g/dL)	3.8 $\pm$ 0.5	3.9 $\pm$ 0.6	0.350
Serum transferrin (mg/dL)	203.8 $\pm$ 45.6	217.1 $\pm$ 41.9	0.200
Staging of disease n (%)			
I	8 (22.2)	9 (24.3)	0.416
II	22 (61.1)	21 (56.8)	
III	6 (16.7)	7 (18.9)	
Type of surgery, n (%)	20 (55.6)	16 (43.2)	
Abdominal rectosigmoidectomy	13 (36.1)	19 (51.4)	
Rectosigmoidectomy with colostomy/ileostomy	3 (8.3)	2 (5.4)	
Right colectomy			

BMI, body mass index; SD, standard deviation; %WL, percentage of weight loss. Synbiotic group vs placebo.  $\chi^2$  test. Student's *t* test.

occurred in the control group (Table 2). There were four cases of anastomotic fistula (10.8%) in the control group.

As for dietary fiber intake during the 7-d intervention period, no significant difference was observed between the groups (mean for the synbiotic group, 13.8  $\pm$  3.2 g; placebo group, 3.3  $\pm$  3.1 g; *P* = 0.72). The first postoperative movement was earlier in the synbiotic group than in the placebo group (1.9  $\pm$  2.8 versus 5.1  $\pm$  4.3 d, *P* < 0.001).

The mean duration of antibiotic usage was lower in the synbiotic group (1.42  $\pm$  0.5 d) than in the placebo group (3.74  $\pm$  4.3 d, *P* < 0.001). The median hospital LOS in the synbiotic group was 3 d (3–5); whereas in the placebo group it was 4 d (3–21; *P* < 0.001). Early discharge is routinely used in our hospital following the Enhanced Recovery After Surgery guidelines [6]. Deaths occurred in three patients in the placebo group because of infectious complications associated with intra-abdominal abscess and fistula formation. Although all deaths occurred in the placebo group, this difference was not statistically significant (*P* = 0.115).

## Discussion

The results of this study demonstrated that the combination of probiotics and prebiotics given orally for 7 d preoperatively in

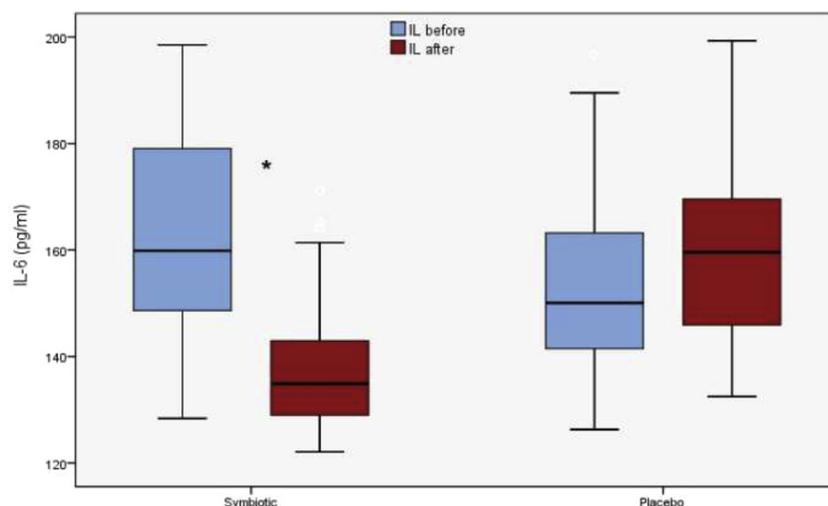
patients undergoing colorectal resection for cancer was able to attenuate the inflammatory state; stimulate intestinal functioning; and reduce complications, antibiotic use, and hospital LOS.

Most of the patients in this study were >60 y of age, in parallel with the demographic transition and global epidemiology. This transition is characterized by increased prevalence and incidence of chronic diseases such as various cancers, both in developed and developing countries [22–24].

We restricted the administration of the synbiotics to the preoperative period, although modern programs such as Enhanced Recovery After Surgery recommend early diet initiation in the immediate postoperative period in many world services, including in our institution. For this reason, we chose not to offer the synbiotic in the postoperative period. In some studies, probiotics were given via a nasogastric tube. However, in our routine, nasogastric tubes are rarely used after colorectal resection. It seems that the potential benefits of the synbiotics are more likely to occur when they are given before surgery. The concept is that preoperative administration would decrease inflammation and stimulate immunologic defenses in preparation of overcoming surgical trauma. Several immunologic and inflammatory markers have been shown to exhibit a better profile in association with probiotic administration [13].

An interesting finding of the present study was the significant reduction of inflammatory markers CRP and IL-6 associated with the use of synbiotics before surgery. The modulation of the intestinal microbiota led to a lower plasma level of cytokines, such as IL-6 [25]. Similarly Zhang et al. [12] reported a significant reduction in IL-6 levels (155.46 versus 178.43 pg/mL) in patients with CRC who received probiotic (*Lactobacillus johnsonii*, 10<sup>8</sup> CFU) for 3 d before surgery and during the postoperative period. In another study, Kotzampassi et al. [26] evaluated the use of probiotics (*L. acidophilus*, *L. plantarum*, *B. lactis*, and *S. boulardii*, 10<sup>9</sup> CFU) given from 1 d before surgery to 14 d after CRC resection in 164 patients. The authors also reported a significant reduction in IL-6 levels [26]. The timing of probiotic use for surgical patients varies in the literature, thus there is no consensus as to when to offer the probiotic. Future studies should determine this timing. The results of reduction in IL-6 levels and CRP during the intervention with synbiotics are consistent with the suggestion that modulation of intestinal microbiota may attenuate the systemic inflammatory response.

The effects of synbiotic administration on the extent of systemic inflammation was assessed using the serum concentrations of both



**Fig. 2.** Mean IL-6 inflammatory marker before and after the intervention between groups. IL, interleukin. \**P* = 0.001 synbiotic before versus synbiotic after intervention.

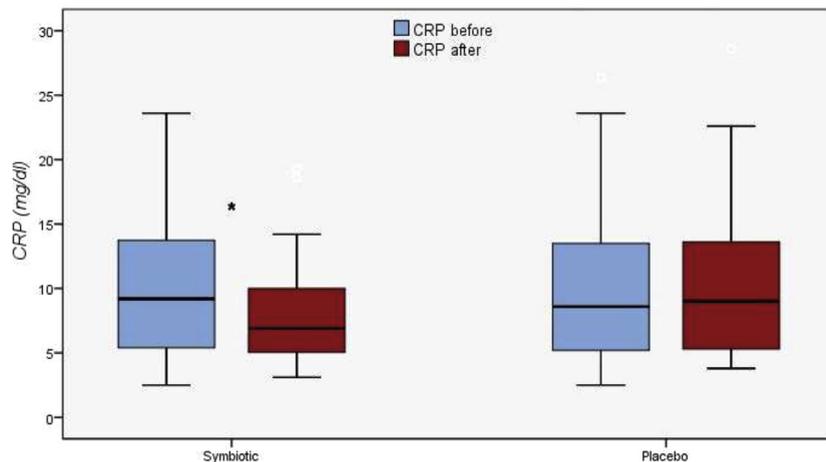


Fig. 3. Mean inflammatory marker CRP before and after the intervention between groups. CRP, C-reactive protein. \* $P=0.001$  CRP before versus CRP after synbiotic use.

IL-6 and CRP. IL-6 is a good marker of activated cytokine cascade, which may include infectious conditions and organ dysfunction. CRP is an acute-phase protein that increases in response to cytokine stimulation, thus it is a marker of inflammation [12]. A healthy intestinal microbiota can stimulate the host immune system and provide better natural defense against invading pathogens. The non-pathogenic intestinal flora protects the intestinal tract from the proliferation of harmful bacteria, especially when the host resistance is decreased. It may be possible that the imbalance of the microbiota induced by surgical stress, bowel preparation, and antibiotics, known as dysbiosis, can be attenuated with the preoperative use of synbiotics. The increase in the number of beneficial bacteria and the reduction of harmful bacteria are important to maintain host defenses, especially during the recovery period from major abdominal surgery [25].

The administration of synbiotics 7 d preoperatively was associated with significant reductions in infectious complications, similar to other studies that have administered probiotics only [9,12,13].

Zhang et al. [12] reported a reduction of infectious complications in patients operated for CRC, from 33.3% in 30 patients in the control group (placebo) to 10% of the 30 patients who received probiotic (*B. longum*, *L. acidophilus*,  $10^8$  CFU) three times daily for 3 to 5 d preoperatively. Similar results were obtained by Kotzampassi et al. [26]. They included 164 patients with CRC to receive a placebo or a combination of probiotics (*L. acidophilus*, *B. lactis*, *Saccharomyces boulardii*  $10^9$  CFU) 1 d before the surgical procedure with an initial loading of four doses with four capsules and 14 d after surgery with a single daily dose. A reduction of any infectious complications in the group with probiotics (11.9%) was reported; whereas in the placebo group, the complication rate was 28.7% ( $P < 0.009$ ). [27]

Table 2

Infectious and non-infectious complications, fiber consumption, time of antibiotic, hospital LOS, and mortality according to groups

Variable	Synbiotic(n=36)	Placebo(n=37)	P-value
Infectious complications (%)	1 (2.8)	7 (18.9)	0.02*
Noninfectious complications (%)	0 (0)	4 (10.8)	0.42
Fiber consumption, mean $\pm$ SD	13.8 $\pm$ 3.2	13.3 $\pm$ 3.1	0.72
Length of antibiotic use, d, mean $\pm$ SD	1.42 $\pm$ 0.5	3.74 $\pm$ 4.3	<0.001
Hospital LOS, d, mean (range)	3 (3–5)	4 (3–21)	<0.001
Mortality (%)	0 (0)	3 (8.1)	0.115

LOS, length of stay; SD, standard deviation.

\* $P < 0.05$  vs control synbiotic.  $\chi^2$  test. Mann–Whitney test.

In another recent study, also controlled by placebo (maltodextrin), which included 150 patients with CRC, the study group received a mix of *L. plantarum*, *L. acidophilus*, and *B. longum* at a dose of  $2.6 \times 10^{14}$  CFU for 16 d (i.e., 6 d before surgery and another 10 d postoperatively). The authors reported a lower incidence of postoperative sepsis in the probiotic group compared with the control group (55 versus 73%,  $P=0.017$ ) [13]. These authors also reported significant reductions in the incidence of central catheter infection, pneumonia, urinary tract infection (UTI), duration of hyperthermia, and cumulative duration of antibiotic usage in patients who received probiotics compared with the control group.

In contrast, in one study, 75 quality CRC patients were randomized to receive placebo or one type of antibiotic (*L. plantarum*) for 10 d before the surgical procedure; prebiotic use was not effective in reducing postoperative complications [28].

Lytvyn et al. [29] conducted a systematic review to assess both the efficacy and safety of probiotics and synbiotics for the prevention of postoperative infections in patients undergoing elective abdominal surgery. They identified 20 trials ( $N = 1374$  participants) reporting postoperative infections. Probiotic or synbiotic use was associated with reduced surgical site infections (SSI; relative risk [RR], 0.63; 95% CI, 0.41–0.98), UTIs (RR, 0.29; 95% CI, 0.15–0.57), and combined infections (RR, 0.49; 95% CI, 0.35–0.70). There was no difference between groups for adverse events (RR, 0.89; 95% CI, 0.61–1.30), respiratory tract infections (RTI; RR, 0.60; 95% CI, 0.36–1.00), LOS (MD: 1.19; 95% CI, 2.94–0.56), or mortality (RR, 1.20; 95% CI, 0.58–2.48). However, they concluded that the currently available evidence is low to very low quality, mainly because of risk for bias and imprecision; thus a large, methodologically sound randomized control trial is needed to corroborate the safety and efficacy of their use in surgical patients.

Recently Kasatpibal et al. [30] conducted a network meta-analysis to estimate the relative effects of probiotic, prebiotic, and synbiotic therapies in reducing SSIs as well as other postoperative complications and to ultimately determine the best regimen to reduce postoperative complications in adult surgical patients. Synbiotic therapy was the best intervention to reduce pneumonia (RR, 0.28; 95% CI, 0.09–0.90), sepsis (RR, 0.09; 95% CI, 0.01–0.94), hospital LOS (mean 9.66 d, 95% CI, 7.60–11.72), and duration of antibiotic administration (mean 5.61 d, 95% CI, 3.19–8.02). Only synbiotic therapy significantly reduced UTIs (RR, 0.27; 95% CI, 0.10–0.73). Probiotic therapy was the best choice to reduce LOS in the intensive care unit. However, no regimen significantly reduced

postoperative mortality in adult surgical patients. This systematic review and network meta-analysis found that synbiotic therapy ranked first over probiotics, prebiotics, antibiotics, normal diet, enteral nutrition, oral neomycin plus bowel preparation, bowel preparation, parenteral nutrition, synbiotics plus oral neomycin plus bowel preparation, and placebo, in reducing SSIs. Based on their findings, they recommend that surgeons should consider the use of synbiotics as an adjunctive therapy to prevent SSIs and other postoperative complications among adult surgical patients. Increasing use of synbiotics might help reduce the use of prophylactic and therapeutic antibiotics.

Rayes et al. [28], in a study with 80 patients undergoing pancreaticoduodenectomy for cancer, reported significant reduction in antibiotics usage with the administration of probiotics in the postoperative period [28]. The group undergoing conventional treatment received antibiotics for an average of 8 d. The mean duration of antibiotic usage in the group that received enteral diet and placebo was 6 d; whereas the group that received enteral diet and probiotic (*Pediococcus pentosaceus*, *Leuconoste mesenteroides*, *L. paracasei*, and *L. plantarum*  $10^{10}$  CFU) reduced the duration of antibiotic treatment to an average of only 4 d. These same authors conducted another randomized, placebo-controlled study in which 95 patients undergoing liver transplantation were divided into three groups, all supplied with early enteral nutrition: standard formula plus selective bowel decontamination, fiber-containing formula plus living *L. plantarum* 299, and fiber-containing formula plus heat-sacrificed *L. plantarum* 299. The authors reported significant reductions in the duration of antibiotic usage during hospitalization, being only 1 d in the study group and 3.8 d in the control group [28].

Liu et al. [13] also reported a reduction in the duration of antibiotic usage associated with probiotics, from 7.56 d in the control group to 6.22 d in the probiotic group. These data are similar to those found in the present study, in which there was a reduction in the time of antibiotic usage in the synbiotic group. We emphasize that all patients received antibiotics. The use of antibiotics is unlikely to have contributed to the complications.

Data from a meta-analysis that evaluated the use of probiotics and synbiotics in elective surgery showed a reduction in hospital LOS with the use of both probiotics and synbiotics [10].

In the study by Liu et al., no deaths were reported in any group [13]. There were three deaths in the present study, all occurring in the control group and all due to abdominal septic complications.

There were several limitations in the present study. It was a single-center study and no microbiologic evaluation was performed to determine an extent in which a microflora intestinal was changed. Also, synbiotic administration was limited to the preoperative period only. Whether and for how long the intestinal microflora remained modulated in the postoperative period remains to be determined.

## Conclusion

The combination of probiotics with prebiotics, administered orally for 7 d preoperatively in patients treated for CRC attenuated the inflammatory state, stimulated bowel function, decreased complications, reduced cumulative duration of antibiotic usage, and shortened hospital LOS. However, considering the wide variation of probiotics associations found in the literature, it is possible to conclude that the ideal association has yet to be determined. Also, it is not clear whether the association of pre- and probiotics, as used in the present study, confers additional advantage over the use of probiotics only.

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