

Observation of postoperative complications in patients that used probiotics in preoperative period of colorectal cancer surgery

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Abstract. *Aim:* Colorectal cancers are prevalent around the world. There may be some complications after cancer related surgeries. This study aims to identify whether the use of probiotics in preoperative period among the patients undergone colorectal cancer surgery diminishes postoperative complications. *Material and Method:* Within the framework of this prospective observational study, the patients, who had colorectal cancer surgery and used probiotics for 5-7 days in preoperative period, were categorised as Group P and the patients, who did not use any probiotics as Group C. The complications in postoperative period and their length of hospital stay were analysed respectively. The patients were followed-up in terms of major complications such as anastomotic leak, anastomotic stricture, surgical site infection, wound infection, wound dehiscence, lung infections, respiratory distress and embolism. *Findings:* A total number of 40 patients were covered under the study. The patients using preoperative probiotics did not develop any anastomotic leak while 4 patients (20%) from the group that did not use any probiotics developed anastomotic leak ($p=0,03$). With regard to the correlation of probiotics use, there has been a decline of 30% in postoperative wound infection (10% vs. 40%, $p<0,028$) and of 45% in lung problems (20% vs. 65%, $p=0,004$). Postoperative ileus was observed 35% less in Group P than Group C. Additionally, the average of hospital stays in such patients diminished at significant level ($17,6\pm 7,3$ days vs $8,8\pm 2,6$, $p<0,001$). *Conclusion:* The use of probiotics in colorectal cancer surgery patients during preoperative period significantly diminishes infectious complications, rate of anastomotic leak incidence and length of hospital stays. It is possible to interpret that the use of probiotics that does not have any apparent side effects in preoperative period reduces the postoperative complications.

Key Words: Preoperative Probiotic Use, Colorectal Surgery, Complications

Introduction

Colorectal cancers (CRC) are one of the most common diseases in the world. Colorectal cancer is the third leading cause of cancer-related deaths (1). There may be some postoperative complications following CRC related surgeries. The most common postoperative complications are anastomosis leak, ileus, intraabdominal abscess and infections. Probiotics are defined as live microbial food additives, which are generated

through being isolated from the bacteria that already exist in human intestinal health and constitute the beneficial microflora, and contribute to human health when consumed at sufficient levels. Probiotics are considered to have a crucial role in the stabilisation of microbiological medium. The previous studies reflected that when used in preoperative and postoperative periods, probiotics majorly improve the intestinal microbial flora, reduce intestinal permeability, downsize infectious complications, use of antibiotics

and length of hospital stay and enhance quality of life among patients (2-4). Probiotics perform such effects through stimulating epithelial growth, mucus secretion and motility, stabilising intestinal barrier and strengthening immunity with various mechanisms (5).

This study aims to investigate whether the use of probiotics in preoperative period among the patients, who underwent surgeries for CRC, diminishes the postoperative complications.

Material and Method

Patient Data

For the purpose of this study, an approval was obtained from the Ethics Committee and the Turkish Medicines and Medical Devices Agency (TMMDA) under the Ministry of Health (Turkey) (Decision No. 08.03.2018- E-18-1844 taken by the University of Health Sciences (SBÜ) Ankara Numune Health Practise and Research Centre Clinical Research Ethics Committee; Decision No. 93189304-514.11.01-E.75051 by the Republic of Turkey, Ministry of Health, TMMDA). The study was conducted as single centre at the General Surgery Clinic of SBÜ Ankara Numune Health Practice and Research Centre between the years of 2017-2018. All applications under the scope of this study were executed in accordance with the latest version of the Declaration of Helsinki and "Good Clinical Practises Guideline". Informed consents were taken from all volunteers, who participated to the study.

This study planned as prospective observational covered 40 patients, who had surgeries due to Colorectal Cancer (CRC). The patients were divided into two groups as probiotics group (Group P), which is comprised of patients that regularly used probiotics with *Lactobacillus Acidophilus*, LA-5 and *Bifidobacterium Animalis* subsp. *Lactis*, BB-12 for 5-7 days in the mornings and nights during preoperative period, and control group (Group C), which is comprised of patients that did not use any probiotics in the last month before their surgeries. After the diagnosis, the preparation for the operation takes approximately

5-7 days. The related literature argues that the use of probiotics for 5-7 days in preoperative period is sufficient to see the effect of probiotics. When the studies on this subject were examined, it was seen that the use of probiotics containing these two bacteria was effective in regulating the intestinal flora (4-5). therefore probiotic product containing these two bacteria was used. The probiotic used in our study was used in capsule form. The recommended method of use was one capsule in the morning and in the evening, therefore the patients used probiotics as recommended.

Prior to the surgery, the age, gender, height, weight, history of co-morbid disease, haemoglobin and albumin levels, if any surgery history, and for probiotic group, the type and dose of probiotics as well as their duration of using probiotics were recorded accordingly. Additionally, the type of surgery and anastomosis were also recorded. In the post-operative period, the complications like wound infection, wound evisceration, anastomosis stricture, intraabdominal abscess, postoperative ileus, urinary infection, lung problems (pulmonary embolism, pneumonia, ARDS, respiratory failure etc.) were documented respectively. The patients were analysed in terms of their length of hospital stay and first one month-mortality rate during post-operative period.

The female and male patients, who were above 18 years old with American Society of Anaesthesiologists (ASA) Score I-III operated with open technique due to CRC, were included under the coverage of study. The patients with immunosuppressive, metastatic, additional malignancy history and uncontrolled comorbidity (ASA Score IV and above), who had previous radiotherapy and chemotherapy history, were not allowed in the study.

Prior to surgery, all patients had bowel preparation via oral laxative lavage. These patients were operated by the same surgical team and the surgery was performed under the standard general anaesthesia. Before anaesthesia, the patients were administered with 1 gr ceftriaxone and 500 mg metronidazole IV as prophylactic antibiotics. The intestinal anastomosis was performed as hand-sewn or with stapler based on the preference of surgeon. A Foley catheter was placed on the inferior part of anastomosis and pelvis as one

for each. Upon the completion of surgery, all patients were submitted to the surgical unit. During the postoperative period, standard fluid therapy was applied for all patients without any enteral nutrition for three days. Three days into postoperative period, patients started the fluid diet with bowel sounds and normal diet with stool. Patients that developed anastomosis leak or ileus did not move to the enteral nutrition and continued with total parental nutrition. 24 hours into postoperative period, the routine antibiotic treatment was not administered, yet infection focused antibiotic treatment was commenced for the patients that developed infection.

Surgical site infection or wound infection were considered in case of any bacterial growth on skin, subcutaneous tissues or intraabdominal, purulent drainage, tissue or fluid samples, and local infection symptoms (i.e. pain, redness, sensitivity). Following 72 hours in postoperative period, the patients without gas-faeces discharge or stool in ostomy were firstly evaluated from radiological aspect with abdominal x-ray in standing position. Where there is a clinical requirement, patients were diagnosed with ileus by computerised tomography (CT). These patients were firstly administered with follow-up and supportive care.

Statistical Analysis

The data were analysed with SPSS (Statistical Package for the Social Sciences, Chicago, IL, USA) 15.0 software. The descriptive statistics reflected continuous variables as mean \pm standard deviation, median (the lowest – the highest), as number and percentage for categorical variables. Kolmogorov Smirnov test was performed to identify whether the distribution of continuous variables is close to normal. T-test was applied to compare the mean values of continuous variables showing normal distribution, and Pearson Chi-Square test for the comparison of categorical data where $p < 0.05$ is considered as significant. Pursuant to the power analysis, the length of hospital stay, which is one of the primary variables, was found as 8.80 ± 2.60 in average for Group P and 17.65 ± 7.34 for Group C while the minimum number of patients for each group was calculated as 20 for $p < 0.001$, $\alpha = 0.99$.

Findings

A total number of 40 patients were grouped into two groups with 20 patients in each group, who use (Group P) and do not use (Group C) probiotics in preoperative period. Among the patients, 13 of them were female and 27 male. The average age was 61.55 ± 14.43 years in Group C and 62.15 ± 12.70 years in Group P, both of which were similar respectively ($p = 0.89$). There has not been any significant difference between two groups in terms of gender distribution ($p = 0.73$). The height, weight and BMI (Body Mass Index) values were identified as similar in both groups ($p > 0.05$). In terms of serum albumin and haemoglobin levels, there has not been any difference between both groups as well.

While 14 of the patients had only hypertension (HT) and 11 diabetes mellitus (DM) as comorbidities, 7 patients had both DM and HT. 7 of the patients had cardiovascular disease background whereas 5 patients had pulmonary disease background. The patients in both groups were similar with regard to their comorbidities ($p > 0.05$).

The average surgery time was found as 144.25 ± 18.15 minutes in Group C and 149.50 ± 28.78 minutes in Group P. However, the difference in both groups is not statistically significant ($p = 0.49$).

In Group C, 5 patients underwent right hemicolectomy, 14 left hemicolectomy and 1 total – subtotal colectomy while in Group P, 7 patients had right hemicolectomy, 9 patients left hemicolectomy and 4 total-subtotal colectomy. In Group K, the anastomosis was hand-sewn in 2 patients and stapler was used in 18 patients. Whereas in Group P, the anastomosis was hand-sewn in 3 patients while 17 patients had stapled anastomosis. Both groups showed similarities in terms of surgical intervention and anastomosis method ($p > 0.05$).

In Group C, 4 patients (20%) developed anastomosis leak in postoperative period whereas no anastomosis leak was observed in Group P. In the follow-up of patients that developed anastomosis leak, it is observed that the leaks healed spontaneously without any revision surgery. Yet, there has been a statistically significant difference between two groups ($p = 0.03$). Moreover, 13 patients from Group

C and 4 patients from Group P developed lung complications in postoperative period. The incidence rate of postoperative lung complications was significantly lower in Group P (20% vs. 65%, $p=0.004$). The incidence rate of pneumonia was higher in Group C than Group P (5% vs. 25%, $p=0.044$). Additionally, 8 patients from Group C and 2 patients from Group P developed wound infection in postoperative period. The rate of wound infection was significantly lower in Group P (10% vs. 40%, $p<0.028$). In Group C, 1 patient developed wound evisceration and 1 patient

anastomotic stricture; yet, wound evisceration and anastomotic stricture were not observed in Group P (Table 1).

In 30 days of postoperative period, the mortality rate was identified as 0% for both groups. The average hospital stay of Group C patients were 17.6 ± 7.3 (5-38) days and 8.8 ± 2.6 (5-13) days in Group P. The length of hospital stay was statistically less in Group P. ($p<0.001$). None of the patients required intensive care. Table 2 summarizes the length of hospital stays in postoperative period.

Table 1. Distribution of Postoperative Complications

	Group C(n=20)	Group P(n=20)	p
Anastomosis Leak	4 (20%)	0 (0%)	*0.03
Lung Problems	13 (65%)	4 (20%)	**0.004
Distribution of Lung Problems			
Pneumonia	5(25%)	1(5%)	0.044
Embolism	2(10%)	0(0%)	
Atelectasis	4(20%)	3(15%)	
Other	2(10%)	0(0%)	
None	7(35%)	16(80%)	
Wound Infection	8 (40%)	2 (10%)	***<0.028
Wound Evisceration	1 (5%)	0 (0%)	0.31
Anastomotic Stricture	1 (5%)	0 (0%)	0.31

* Rate of anastomosis leak, Group P ($p=0.03$)

** Incidence rate of lung problems, Group P ($p=0.004$)

*** Wound infection rate, Group P ($p<0.028$)

Table 2. Postoperative length of hospital stays (day)

Group	n	Mean \pm SD	Median	The Lowest	The Highest	*p
Group C	20	17.6 ± 7.3	16	5	38	<0.001
Group P	20	8.8 ± 2.6	9	5	13	

n; number of patients.

* Average length of hospital stay, Group P ($p<0.001$).

Discussion

In consideration with the study, it is identified that the use of probiotics for 5-7 days in preoperative period of patients, who undergone CRC surgery, may diminish the incidence rate of infectious and non-infectious complications that are clinically observed in postoperative period, and may significantly shorten the length of hospital stays. The related literature argues that the use of probiotics for 5-7 days in preoperative period is sufficient to see the effect of probiotics.

A number of laboratory studies described the effect mechanisms of probiotics and reflected their effects in preventing bacterial translocation and immunomodulatory effect. Unlike such effects, the aim in this study is to analyse the clinical contribution of probiotics and their effect on incidence rate of complications. Within the scope of this study, the patients that used probiotics in preoperative period did not develop any anastomosis leak while 4 patients (20%) from the group that did not use any probiotics developed anastomosis leak. The use of probiotics diminished the incidence rate of postoperative wound infection by 30% (10% vs. 40%) and incidence rate of lung problems by 45% (20% vs. 65%). Moreover, the incidence rate of early postoperative ileus was lower in patients using probiotics (15% vs. 50%). Consequently, the average length of hospital stays among such patients significantly shortened as well (17.6 ± 7.3 day vs. 8.8 ± 2.6).

It is known that probiotics cause effect through various mechanisms like in foods with pathogens, race for erythrocyte adhesions, degradation of toxins, antimicrobial factor growth and immunomodulation (6). Probiotics are considered to reduce postoperative complications by inhibiting bacterial translocation with the aforementioned mechanisms (7). The recent studies conducted on animals and humans concluded that probiotics have a potential role in terms of inhibiting postoperative complications among the patients, who underwent major gastrointestinal surgeries (8) (9). Moreover, the results from experimental studies support the data regarding that probiotics reduce the postoperative complications. The animal study by Seehofer et.al reflected that bacterial and mesenteric

lymph nodes significantly decreased when rats were administered with probiotics, and animals that had a high cecal concentration had less translocation (10). Another study by Dock et.al indicated that rats with mucosal atrophy due to a three-day fasting recovered fast after the surgery upon given with probiotics as well as the lessen mucosal atrophy showed a fast improvement (11). Similarly, a study by Lu et.al conducted with 30 volunteers that used probiotics containing *Lactobacillus Rhamnosus* showed that the anaerobic bacteria/aerobic bacteria counts in faeces increased and simultaneously IL-1 and TNF- α values decreased. The same study reflected that the subjects showed good tolerance to probiotics without any side effects (12). All of such studies present the effect mechanisms of probiotics in preventing complications.

Pneumonia developed in postoperative period is crucial among the complications (13). The lung failures that occur in postoperative period are the most significant morbidity and mortality reasons with an incidence rate of between 5-80% based on patients, hospitals and type of surgery (14) (15). The meta-analysis published by He et.al concluded that the use of probiotics as prophylactic in patients undergoing colon resection due to Colon Cancer(CC) diminished the incidence of pneumonia in postoperative period (16). In consideration of our study, the incidence rate of postoperative lung problems is 65% in control group and 20% in probiotics group; whereas the incidence rate of pneumonia was found higher in control group than the group using probiotics (5% vs. 20%). Regardless of elaborating on the factor of pneumonia, our study delivered that probiotics reduce the emergence of pneumonia in postoperative period by diminishing bacterial translocation and strengthening immune system.

Surgical site infections are related with the surgery itself and patient's additional risk factors. The most significant causes are skin, mucosa and gut flora. Additionally, surgical team, operating theatre and surgical instruments may be the other reasons of surgical site infections (17). In our study, the surgical site infection was 40% in control group and 10% in probiotics group. Other than the surgical site infection, there has not been any deep incisional surgical site infection in

both of the groups. Considering that the clinical features of patients, surgery performance sites, surgical team and surgical techniques were similar among the patients, it is possible to say that the use of probiotics significantly diminished the surgical site infection.

In a clinical study by Rayes et.al, they divided patients that had major abdominal surgery based on their post-operative nutrition regime where they provided first group patients with total parenteral nutrition or fibre-free enteral nutrition, second group with enteral fibre-containing nutrition with living *Lactobacillus* and third group with enteral fibre-containing nutrition with heat-killed *Lactobacillus* in order to analyse post-operative development of bacterial infection, durations of antibiotic therapy and hospital stay, non-infectious complications, side effects of the nutrition and onset of bowel movement. Consequently, the incidence of infections was found lower in group 2 and 3, and the duration of antibiotic therapy was shorter in patients with enteral nutrition containing living *Lactobacillus*. The difference in the length of hospital stay and incidence of non-infectious complications was not significant (18). The study by Kanazawa et.al analysed the postoperative infectious complications like surgical site infection, peritoneal abscess and sepsis in biliary cancer patients by including probiotics and prebiotics to enteral nutrition. It is emphasized that the patients receiving probiotics had less infectious complications, shorter antibiotics therapy and higher quality of life with early discharge from the hospital (3). The results of our study support the outcomes of aforementioned studies.

Katerina et.al analysed the effect of formulation with four different probiotics on the minimization of complications among the patients undergone colorectal surgery. As a result, there has been a significant decrease in postoperative pneumonia (11.3% vs. 2.4%), surgical site infection (20% vs. 7.1%) and anastomotic leak (8.8% vs. 1,2%) between the group administered with probiotics and not administered with probiotics respectively (19). Unlike our study, a probiotic formulation with four microorganisms was used, and probiotics were mainly used in postoperative period rather than preoperative period. Despite of differences in methodology, the related study – similar to

our study- reflected that there has been a significantly decrease in lung problems, surgical site infection and anastomotic leak. The comprehensive study by Liu et.al where they compared patients using probiotic and control group and reflected that the probiotics group showed an improvement in postoperative peristalsis, incidence of diarrhoea and infectious complications (20).

Within the framework of our study, the patients in both groups with anastomotic leak and stricture, wound infection and ileus that identified radiologically did not required further surgery and recovered with conservative treatment and follow-up. However; such treatments extended the length of hospital stay and increased medical expenses. The longer hospital stays cause also delays in postoperative medical oncology treatment process. The relief in complications and shorter hospital stays with the use of probiotics both reduce medical expenses and prevent any delay in the commencement of postoperative medical oncology treatment.

In conclusion, this study reflected that the use of probiotics in preoperative period significantly reduces the incidence rate of postoperative complications in patients who underwent colorectal surgery. However, some limitations should be noted. First, we were unable to randomize the patients. Because we planned the study as observational study. Second, Only 40 patients were included in the study, because we had limited time to complete the study. Third; we included patients who underwent open technique surgery, because only patients operated with open technique used probiotic support.

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AUTHOR CONTRIBUTIONS

Dr Ahmet Soykurt who is a doctor in, Near East University Hospital, Department of General Surgery. Dr Ahmet Soykurt takes part in all process of the study.