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Usage of Probiotics and its Clinical Significance at Surgically Treated Patients Suffering from Colorectal Carcinoma

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ABSTRACT

Introduction: Colorectal Cancer (CRC) is the third most common malignant disease and the fourth most common cause of death associated with malignancy. Adenocarcinomas account for 95% of all cases of colon cancer. Treatment usually includes a surgical resection which is preceded or followed by chemotherapy and radiotherapy depending on the stage. There is constant interest in the microbiological ecosystem of the intestine, which is considered to be crucial for the onset and progression of the disease as well as the development of postoperative complications. Iatrogenic factors associated with the treatment of CRC may result in pronounced expression of virulence of the bacterial intestinal flora and fulminant inflammatory response of the host which ultimately leads to adverse treatment results. The modulation of intestinal microflora by probiotics seems to be an effective method of reducing complications in surgical patients. The question is whether ordering probiotics can lead to more favourable treatment outcomes for our patients who are operated due to colorectal adenocarcinoma, and whether this should become common practice. **Aim:** To demonstrate the clinical significance of probiotic administration in patients treated for colorectal adenocarcinoma and the results compared with relevant studies.

Patients and Methods: In a randomized controlled prospective study conducted at the Clinic of General and Abdominal Surgery of the UCCS in the period of 01 January 2017 until 31 December 2017, there were a total of 78 patients with colorectal adenocarcinoma. Patients were divided into two groups: a group treated with oral probiotics (n = 39) according to the 2x1 scheme starting from the third postoperative day lasting for the next thirty days, followed by 1x1 lasting for two weeks in each subsequent month to one year, and the control group (n = 39) which was not routinely treated with probiotics. **Results:** A statistically significant difference in the benefit of using probiotics was found during postoperative hospitalization and the occurrence of fatal outcome in the first six months. All complications were more present in the group of patients untreated with probiotic, with statistical significance shown only in the case of ileus. Probiotic has a statistically significant reduction in postoperative complications in the localization of tumours on the rectum -33.3% and the ascending colon -16.7%. **Conclusion:** There is a significant benefit of administering probiotics in surgically treated patients for colorectal adenocarcinoma.

Keywords: colorectal cancer, probiotics, surgical complications, colon surgery.

1. INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and the fourth most common cause of death associated with malignancy, and its frequency increases year by year. The probability of colorectal cancer is around 4%-5%, and the risk of CRC development is associated with age, history of chronic diseases and lifestyle. Adenocarcinomas account for 95% of all cases of colon cancer (1, 2). The most common postoperative surgical complications after colorectal cancer resections are infection at the site (Surgical site infection), anastomosis loosening, intra-ab-

dominal abscess, ileus and bleeding. These complications directly affect the outcome of treatment and must be diagnosed accurately (3).

In open colorectal surgery, the incidence of SSI varies from 2-25% and is associated with BMI ≥ 30 , by performing or submerging stomas, perioperative transfusion, male sex, ASA score $\geq III$, and wound contamination (4, 5). SSI usually occurs within 30 days of surgery. By analysing the available medical literature, we found that the use of probiotics reduces the risk of infection in patients undergoing CRC surgery. It has been found that the combination of more

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than one micro-organism, such as *Lactobacillus* and *Bifidobacterium*, improves treatment and surgical recovery (6).

Anastomotic loosening is the most severe complication associated with intestinal surgery and ranges from 2.9% to 15.3%. At least one third of mortality after colorectal surgery is attributed to the anastomotic loosening (7). Due to the seriousness of complications associated with anastomotic loosening, it is necessary to identify the problem and act accordingly.

Postoperative ileus (POI) has long been regarded as an inevitable consequence of gastrointestinal surgery. It extends hospital stay, increases morbidity and increases the cost of treatment. The paralytic postoperative ileus is conventionally cured by the restriction of the use of narcotics and the administration of NSAID's and local anaesthetics. Electrolyte correction is also an important factor to be considered (8). According to the recent data from the literature, ileus that lasts longer than 6 days serves as a better clinical definition of the extended POI, what we have respected and applied through our research (9). There are certain predictions in the available literature that speak in favour of the possible effect of probiotics on the development of intestinal motility, and accordingly, in our work, we investigate the possibility of such an effect.

Since host surgical manipulations are part of everyday surgical practice in an abdominal surgery, it is very important to examine the mechanisms and effects of changes in intestinal microflora on the results of treatment (10). In patients operated due to colorectal cancer, there is not only surgical stress, but also a series of perioperative interventions imposed by modern therapy, including preoperative cleansing of the intestines, multiple exposure to antibiotics, prolonged starvation, exclusively intravenous nutrition, administration of vasoactive agents, proton pump inhibitors and opioids; and in the end, intense manipulation that can disrupt the host-microbial relationship, and thus bacteria can give a pronounced expression of virulence and fulminant inflammatory response within the host (11, 12). There are several important mechanisms about the positive effects of probiotics: modification of the gut microbiome, competitive adhesion to the mucous membranes and epithelium, strengthening of the bowel epithelium barrier and modulation of the immune system in order to give priority to the host. Changes in intestinal flora caused by the administration of probiotics can result in changes in the metabolite of bacterial fermentation and improved intestinal motility, which can be attributed to the decrease in pH which leads to a shortening of transit time of intestinal contents. The latest research deals with the relationships within the microbial-brain-axis and the effects of various probiotics on the respective axis (13). The occurrence of complications after surgical treatment for colorectal cancer is a serious problem that results in a significant increase in morbidity and mortality and an economic impact increase (6). Great efforts are being made to improve the outcome of treatment in these patients around the world. The latest guidelines have con-

tributed to a significant improvement in the final outcome of the treatment of patients suffering from CRC, but it remains a major issue to be addressed at all surgical institutions (6). The question that arises is whether the administration of probiotics can lead to a more favourable outcome in our patients treated due to colorectal adenocarcinoma, and should this become a common practice?

2. AIM

The aim of the study is to demonstrate the possible impact of probiotic administration on one-year treatment results in patients treated for colorectal adenocarcinoma and the results compared with relevant studies.

3. MATERIAL AND METHODS

In a randomized controlled prospective study conducted at the Clinic of General and Abdominal Surgery of the UCCS, in the period from 01.01.2017 to 31.12.2017, a total of 78 patients with colorectal adenocarcinoma satisfying the listed inclusion factors were classified into two groups.

Group treated with oral probiotic (n = 39) according to the scheme 2x1 capsules from the third postoperative day during the next thirty days, and then 1x1 for two weeks each next month to a total of one year. The ordained probiotic contains eight bacterial cultures (*Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus plantarum*, *Lactobacillus rhamnosus*, *Bifidobacterium lactis*, *Bifidobacterium bifidum*, *Bifidobacterium breve*, *Streptococcus thermophilus*). The control group (n = 39) was not routinely treated with probiotics. Patients from both groups were introduced a liquid diet per day after the third postoperative day in terms of 2dL clear water, after that period the diet was ordained depending on the objective signs of a harmonious motility of the gastrointestinal tract. During chemotherapy for symptomatic treatment of diarrhoea, patients from both groups received loperamide. Loperamide is a derivative of haloperidol with exclusive local action on the intestinal wall, in a way that slows down the peristalsis of diarrhoea. Ethical approval was obtained from Ethical Committee University clinical center of Sarajevo.

3.1 Inclusion factors

Pathohistologically proven colorectal adenocarcinoma

- Karnofsky index $\geq 80\%$,
- ASA score ≤ 3 ,
- Patients without significant cardiac and neurological comorbidity,
- Normal values of preoperative albumin,
- Stage III (tumour have spread to surrounding lymph nodes, but not to other organs, therapy: surgery, i.e. segmental resection, and then KT and possibly RT),
- Patients who have undergone one of the standard surgical procedures with an open approach for the treatment of colorectal cancer,
- Patients operated in the elective program.

4. RESULTS

Only one fatal outcome (1 or 1.3% of the total sample) was recorded, in the group of non-probiotic patients. An analysis of Fisher's exact test indicates that there is no significant difference in the presence of fatal outcomes in the hospital relative to the use of probiotics ($p > 0.05$) (Table 1).

All complications were more present in the group of patients not treated with probiotics, but statistically significant difference was confirmed only in the case of ileus ($p < 0.05$) (Table 2).

Student's T-test shows that there is a significant difference in the duration of postoperative hospitalization in the group of patients treated with probiotic compared to the control group ($p < 0.05$).

In addition to the statistically significant difference in the group of patients not treated with probiotics, mortality was recorded during the first 6 months after surgery. A total of 2 (5.1%) cases of death were reported in the group of patients treated with probiotics, 7-12 months after the operation.

Statistically, a higher probability of occurrence in a non-treated probiotic group compared to a probiotic-treated group has only ileus with OR 2.43 (CI 1.85-2.98). SSI has approximately 1.5x higher probability of occurrence in patients who have not been treated with probiotics. The anastomotic loosening as an independent variable has almost the same occurrence regardless of the use of probiotic 1,001 (Table 3).

The largest reduction in postoperative complications in the group of patients treated with probiotics was in the rectal region -33.3% and ascending colon -16.7%, with statistical significance. They are followed by a sigmoid colon with a decrease of -12.5%.

5. DISCUSSION

One of the key findings in our study was that all complications were more present in no probiotics group but a statistically significant difference was only demonstrated in the case of ileus ($p < 0.05$) that we defined as the absence of signs of intestinal peristalsis longer than six postoperative days. If we consider the possible mechanism of other observed complications, an inescapable aspect of anastomotic loosening and intraabdominal abscess is the prolonged postoperative ileus. Tests in patients who underwent elective colectomy and subsequently developed postoperative ileus showed that patients were significantly more likely to suffer other postoperative complications (14). Due to impossibility of bowel movement, there is an increasing amount of air and fluid accumulation in the gut. From a mechanical perspective, this leads to distension of the intestinal wall which compromises its own intestinal circulation, which is in favour of anastomotic loosening. Also, inadequate absorption from the

Treatment outcome		Patients treated with probiotics	Patients which were not treated with probiotics	Total
		Discharged	39 (100.0%)	38 (97.4%)
Mortal outcome		0 (0.0%)	1 (2.6%)	1 (1.3%)
Total		39 (50.0%)	78 (100.0%)	

Table 1. Final outcome of treatment in relation to the use of probiotics. $\chi=1.013$; $p=0.500$

Postoperative complications		Patients treated with probiotics	Patients which were not treated with probiotics	Total
		SSI $\chi=0,530$; $p=0,682$	11 (28.2%)	14 (35.9%)
Anastomosis loosening $\chi=1,412$; $p=0,431$		2 (5.1%)	5 (12.8%)	7 (9.0%)
Ileus $\chi=7,341$; $p=0,007$		1 (2.6%)	9 (23.1%)	10 (12.8%)
Intraabdominal abscess $\chi=0,394$; $p=0,530$		5 (12.8%)	7 (17.9%)	12 (15.4%)

Table 2. Frequency of postoperative complications in relation to probiotic treatment

Variables in equation						
	OR	S.E.	Wald	df	Sig.	95% CI
SSI	1.425	.488	.528	1	.467	-1.245-5.412
Anastomosis loosening	1.001	.870	1.324	1	.250	1.586-3.241
Ileus	2.430	1.082	5.059	1	.025	1.854-2.985
Intraabdominal abscess	0.487	.635	.391	1	.532	-0.254-4.258

Table 3. Multivariate regression analysis of complications in relation to ordinary probiotics

intestine and delayed start of the diet causes the general weakness of the organism, and ultimately adds to the aforementioned mechanical aspect of anastomosis loosening and enhances it. This is followed by the conclusion of our study, which is that by administering probiotics we actually reduce postoperative morbidity and the result obtained supports a positive hypothesis of research. In the study of Verde Elena et al. regarding the effect of probiotics on the intestinal motility that the critical value of the intestinal microflora was shown to be the same. Disruption of the intestinal microbiome by infectious agents, antibiotics, and mechanical manipulation leads to disobedience in terms of retroperistalsis established at 50% of the monitoring time in the study performed on the experimental mice (15).

Rhee SH and others in their research on the axis of the intestine-brain found that intestinal luminal microflora, immune system, enteric nervous system and central nervous system are interconnected and that together, among other functions, they control bowel motility. However, most of the evidence has been derived from animal studies, and their effect in humans is unclear due to a small number of studies on humans (16).

In a review of Eirini's 2017 study, which sums up the current research on the field of probiotic effects on intes-

tinal motility, it has been concluded that further studies on the subject of probiotic species and strains are needed in the future and that the dose and duration of treatment are particularly effective at intestinal motility in different intestinal pathologies (17). In our work we have demonstrated that the selected available combination of bacteria acts positively in patients who have been treated for colorectal cancer in our Clinic. Each hospital institution has certain written or unwritten criteria when it comes to discharge a patient. J. F. Fiore et al. have written a review on the subject of existing criteria for discharge patients treated with surgery for colorectal cancer. They concluded that most studies applied a combination of three or four criteria, most commonly referred to: tolerance of oral intake (80%), recovery of bowel function (70%), appropriate pain control (44%) and appropriate mobility (35%). The endpoints for determining the criteria are generally poorly defined in the literature (18). In our study, we found that patients treated with probiotics were postoperatively significantly shorter hospitalized in relation to the control group. Our hospital discharge criteria matches the criteria set out in the study. According to Pitsouni et al., length of hospital stay and the length of receiving antibiotic therapy in patients who received probiotics were significantly reduced (19). From a clinical point of view, this is important because shorter antibiotic regimens reduce the risk of antibiotic resistance. Short hospital stay reduces the risk of intra-hospital infection and reduces the costs. Taking into account that in our study, patients treated with probiotics had at the same time several other complications, we can rightly conclude that this result of decreasing postoperative hospitalization also supports a positive hypothesis of probiotic-effect research.

During the surgery 6 months follow-up period, there was a statistically significant difference in the non-probiotic group, deaths were recorded in relation to patients treated with probiotics. An analysis of 32,000 patients from the ACS National ACS NSQIP (ACS National Surgical Quality Improvement Program) showed that mortality was four times more common in patients with colectomy who developed postoperative ileus compared to patients without ileus (4% versus 1%, $p < 0.001$) (20). By administering probiotics in our study, we obtained a statistically significant reduction in the incidence of postoperative ileus, which, if relying on the conclusions from the study, significantly reduces mortality after colorectal surgery. Similarly, the retrospective study of the causes of mortality after colorectal carcinoma surgery showed a high mortality rate (> 50%) in patients who had a colectomy for colon cancer, with the following complications: coma, cardiac arrest, vascular prosthesis failure, kidney failure, pulmonary embolism and progressive renal insufficiency (21). Other studies were concerned with the assessment of failure of treatment and mortality after the need for reoperation due to anastomosis. One study looked at patients who had any GI anastomosis (colorectal, oesophageal, pancreatic, small intestine) and found that patients suffering from postoperative anastomosis loosening had greater mortality within the first 30 post-

operative days (8.4% according to 2.5%, $p < 0.0001$) and long-term mortality (36.4% versus 20.0%, $p < 0.0001$) compared to patients without loosening of anastomosis (22). Administration of probiotics in our study showed a numerical decrease in the occurrence of anastomosis loosening in relation to the control group. In a multivariate regression analysis, loosening of anastomosis has the same incidence (OR = 1,001), regardless of the use of probiotics. However, if we look at the occurrence of anastomosis loosening in a group of patients untreated probiotics with ileus, it is clear that postoperative ileus can be considered as one of the probable causes of anastomosis loosening. In the group of patients treated with probiotics, only one case of the occurrence of postoperative ileus was recorded.

In our study, SSI and intra-abdominal abscesses have approximately 1.5 times more probability of occurrence in patients which were not treated with probiotic, and although it does not show statistical significance, we have come to the assumption that post-operative probiotic therapy could reduce the frequency of SSI. In a study designed to investigate the effect of perioperative probiotic use on the immune response, intestinal microbiome and surgical outcome of patients treated for colorectal cancer, oral probiotics have been shown to be a positive predictive factor for reducing SSI (23). The intraabdominal abscess in the study was observed primarily as a result of anastomosis loosening, more precisely ileus, which in multivariate regression analysis showed a statistically significantly higher probability of occurrence in a group that was not treated with probiotics compared to a group treated with probiotic OR 2.43 (CI 1, 85 to 2.98).

The greatest effect on the reduction of postoperative complications in the group of patients treated with probiotics is in the rectal region -33.3%, then in the ascending colon region -16.7% and then the sigmoid colon -12.5%. Available medical literature does not have the same or similar results with which we could compare this interesting result. The presumption of significant reduction of complications in the rectal region and the sigmoid colon is precisely the effect on the consistency of the stool, its qualitative composition and the time of movement through the intestine, which precisely encompasses the scope of probiotic activity. Resection of the right half of the colon, which is largely responsible for the absorption of water and electrolyte, results in malnutrition and diarrhoea. In addition to improving nutritional status by alleviating the effects of diarrhoea, there is growing evidence that probiotics can be used to improve the absorption of protein, vitamin B and micronutrients (such as calcium and iron) from food intake (23). In this way, we explain the positive effect of probiotics on statistically significant reduction of tumour complications in this region. In conclusion, there is evidence that a healthy microbiome stimulates better recovery and improves the overall and local status of the patient. Which probiotic, in which therapeutic scheme, how long and when to give or not give it remains the subject of further research.

6. CONCLUSIONS

Based on the formulation and definition of the problem, the objectives and the tasks of the research, the hypothesis set and the obtained results, the following conclusions can be drawn:

Compared to postoperative morbidity (postoperative complication), the assumption is that there is a greater presence of complications in the group of patients unprotected with probiotics compared to treated ones, and statistically significant differences exist only in the case of ileus 2.43 times more frequently in a group of untreated probiotic patients. Therefore, a part of the primary (positive) hypothesis is accepted which states that there is a statistically significant difference in the frequency of postoperative complications in patients treated with probiotics compared to untreated ones.

SSI has approximately 1.5 times higher probability of occurrence in patients untreated with probiotics.

In the first six months of postoperative monitoring, statistically, a smaller number of deaths occurred in patients treated with probiotics compared to the control group.

Patients treated with probiotics had fewer days of postoperative hospitalization compared to patients untreated with probiotics and a statistically significant difference ($p < 0.05$).

Probiotics proved to be of particular importance in reducing postoperative complications when administered during localization of tumours in the rectal region (-33%), then in the region of ascending colon (-16.7%), and the sigmoid colon (-12.5%), we consider that it would be of particular importance to introduce routine administering of probiotics in these tumour localizations.

- **Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent forms
- **Author's contribution:** S.B. and E.H. gave substantial contribution to the conception or design of the work and in the acquisition, analysis and interpretation of data for the work. Each author had role in drafting the work and revising it critically for important intellectual content. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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