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THE EFFECTS OF NUTRITIONAL SUPPORT ON SELECTED LABORATORY PARAMETERS IN PATIENTS WITH COLORECTAL CANCER UNDERGOING SURGICAL RESECTION OF THE COLON

Mária Servátková, Peter Chlebo, Zuzana Chlebová

ABSTRACT
The benefit of the nutritional support provided to patients with colorectal cancer who have undergone the planned resection of the colon in relation to the laboratory markers of nutrition was examined. And it is currently being discussed, that pre-operative optimization of nutritional status reduces the incidence of post-operative complications in cancer patients and regulates selected laboratory parameters. This was a retrospective study where the treatment group (n = 52) received the enteral nutritional support 21 days before the scheduled surgery and the other group was formed of patients without preoperative enteral nutrition (n = 52). Laboratory parameters (CRP, leukocytes, albumin, total proteins) were monitored for at least one month before the planned surgery and just before the operation, and the effect of supplemental enteral nutrition on selected laboratory parameters between these two groups was compared. In a group of patients with enteral nutrition, serum albumin levels increased significantly, while CRP was significantly reduced during preoperative enteral nutrition (albumin S-ALB from 35.42 to 37.48, p = 0.0008, C reactive protein from 26.5 to 14.092, p = 0.0007). Nutritional support 21 days before surgery in oncological patients resulted in an improvement in laboratory parameters compared to the group of patients without nutritional enteric support. Malnutrition in patients who are candidates for major surgical intervention is a risk factor for postoperative morbidity and mortality. However, further studies are required to verify the effectiveness of this early nutritional intervention on medium and long-term clinical parameters in different types of cancer.

Keywords: nutridrink; enteral nutrition; malnutrition; colon; hypoalbuminemia

INTRODUCTION
Cancer of the colon and rectum is one of the most commonly diagnosed cancers in the world **(Torre et al., 2015)**. Although patients with early colorectal cancer could be successfully treated with surgical procedures, the large surgery itself may cause the dysfunction of homeostasis, defensive mechanisms, and inflammatory response, which may increase the rate of postoperative complications and extended hospital stay. Nutritional status is a key factor affecting clinical outcomes in patients **(Xu et al., 2018)**. Unintentional weight loss in cancer patients is an alarming constitutional change predicting the progress of the illness and shortened survival time **(Chow et al., 2020)**. It is important to provide nutritional support administered through enteral nutrition or parenteral nutrition **(Chow et al., 2020)**. Historically these approaches are accompanied by concerns with increased complications and costs. Therefore, enteral nutrition can be the preferred form due to its lower costs, less complications, and improved results **(Altintas et al., 2011)**.

Scientific hypothesis
We examine in our study, whether the administration of Nutridrink compact rises the level of albumin and lowers the level of C-reactive protein in patients with colon cancer before the planned surgery.

MATERIAL AND METHODOLOGY
Study design
The study was a retrospective one focused on individual cases that used the database of the surgical department of the Topoľčany city hospital in Slovakia. Data were collected from medical documentation of surgical department patients, including basic characteristics, laboratory, and perioperative data. This study was approved by the Ethics Commission of the Institute – World of Health, hospital Topoľčany. In Topoľčany hospital, it is recommended that patients with colorectal cancer should take enteric nutrition as part of preoperative optimisation of the nutritional condition before the planned colon resection.

Patient selection

The study ran from September 2015 to September 2019 and the criteria for patient spooling were as follows: age between 18 – 90 years, the diagnosis of colorectal cancer, the patient was subjected to a colorectal surgical procedure. All patients signed informed consent. The exclusive criteria were as follows: inadequate data on the patient for analysis, disapproval of the patient, non-compliance with the treatment regimen, patients who have undergone much greater surgical performance than originally planned, and patients who had already had a stoma and have previously undergone surgery for colorectal cancer, patients who have had a renal and hepatic failure, inability to consume food orally, psychiatric disorders, pregnancy, uncontrolled infection, and all patients who did not have the criteria for inclusion.

Grouping

In our database, 142 patients were identified, of which 38 patients were excluded because they did not meet the criteria for inclusion and had incomplete medical documentation and the remaining patients were divided into two groups. The treatment group was formed by 52 probants who accepted the proposal of the treating surgeon and received commercially available nutrition (Nutridrink Compact) at least 21 days before the planned surgical procedure as an addition to a normal rational diet. The patient's cooperation is an important factor in the treatment of enteral nutrition. Many patients poorly tolerate enteral nutrition and refuse to leave their normal diet. This resulted in a control group of patients who formed 52 probants who had rational nourishment as usual, and were verbally guided for nutrition.

Preoperative nutrition

Patients received Nutridrink Compact (Nutricia) as an addition to a normal rational diet, it is a high-energy nutritionally complete liquid designed for a dietetic procedure for malnutrition that is related to the disease. The content of Nutridrink is mentioned in Table 1.

Clinical evaluation

The following data were collected: body weight, height, a general state of health, age, gender, family status, degree of education, the onset of disease, number of symptoms, metastasis, co-morbidity.

Laboratory evaluation

The course of sampling is an important prerequisite for an objective assessment of the patient´s health. The sampling from the patient was realized once by a qualified nurse. Venous sampling was done in the morning after 8 – 12 hours long fasting. The patient was allowed to drink only a small amount of clear water. The blood sample was taken from the peripheral vein of the upper limb. The skin was disinfected with eighty percent ethanol. The blood was taken into the vacuum test tube, the test tube was filled to the mark and subsequently, the sample was mixed and labeled with the personal data of the patient. The material was transported into the laboratory of the company Medirex. The company Medirex is a holder of a certificate of conducting STN EN ISO 9001:2009 and simultaneously of the needed sampling certifications for individual examinations, namely hematological and biochemical. Subsequently, the result of the examination of the patient was recorded into the patient´s medical record.

Blood count, C-reactive protein, albumin, total proteins, and glycemia were recorded.

Assessment of the status of nutrition

Blood was collected minimally one month before the planned operation in both groups. In the treatment group, a high-energy nutritional supplement was added to the patient's rational diet for at least 21 days. Subsequently, blood was collected again just before surgery. The patient's weight was determined at least one month before surgery and the second time just before surgery in both patient groups.

Surgical procedures

The surgery was performed by one surgeon who specializes in the given disease of the colon by laparotomic and laparoscopic surgical techniques. The anastomosis was end-to-end or side-to-side depending on the location and the decision of the surgeon.

Statistical analysis

Statistical analysis was performed using Microsoft Excel 2010. Quantitative data are expressed as mean ± standard deviation and compared with the t-test. *p*-value $p < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

A total of 142 patients were analysed, 38 were excluded because they did not meet the desired criteria for patient selection for our study, and subsequently 104 patients underwent evaluation.

The main characteristics are listed in Table 2. The female gender was 48.08% (n = 25) and male 51.92% (n = 27) in the treatment group. In the control group the female gender was 44.23% (n = 23) and male 55.77% (n = 29). The average age in the first group was 57.46 ±7.92 years and in the control group 57.92 ±8.27 years. Patients were most commonly married, 57.69% (n = 30) and 53.85% (n = 28) in the control group. The majority of patients in the treatment group completed secondary education, 73.07% (n = 38) and 80.76% (n = 42) in the control group.

The clinical characteristics of patients are mentioned in Table 3. The onset of the disease was noted just before surgery, where the first group of patients had symptoms at 57.69% (n = 30) 4 – 6 months ago, at 23.07% (n = 20) 7 – 12 months ago, at 9.61% (n = 5) 0 – 3 months ago, for 9.61% (n = 5) over 13 months ago. In the control group, 21.15% (n = 11) 0 – 3 months ago, 11.53% (n = 6) 4 – 6 months ago, 53.85% (n = 28) 7 – 12 months ago and 13.46% (n = 7) over 13 months ago. The most common stage of colorectal carcinoma reported prior to surgery was the stage II in the treatment group, 48.07% (n = 25), Stage I 19.23% (n = 10), Stage IV 19.23% (n = 10) and Stage III 13.46% (n = 7). In the control group the stage I 13.46% (n = 7), Stage II 19.23% (n = 10), Stage III 48.07% (n = 25) and stage IV 19.23% (n = 10).

Table 1 Nutritional composition of Nutridrink compact.

Energy value	1010 kJ	Minerals and trace elements	
kcal	240	Na	96 mg
Fats (35 En%)	9.3 g	K	236 mg
of this		Cl	91 mg
Saturated fatty acids	0.9 g	Ca	174 mg
Carbohydrates (49 En%)	29.7 g	P	174 mg
of this		Mg	33 mg
Sugars	15.0 g	Fe	3.8 mg
Lactosis	<0.5 g	Zn	2.9 mg
Fiber (0 En%)	0 g	Cu	0.43 mg
Proteins (16 En%)	9.6 g	Mn	0.80 mg
Salt	0.24 g	F	0.20 mg
Vitamins		Mo	24 μg
Vit A	240 μg RE	Se	14 μg
Vit D_3	1.8 μg	Cr	16 μg
Vit E	3.0 mg-α-TE	I	32 μg
Vit K	13 μg	Other	
Thiamine	0.40 mg	Choline	88 mg
Riboflavin	0.40 mg	Osmolarity	790 $mOsmol.L^{-1}$
Niacin (4.3 mg-NE)	2.2 mg		
Pantothenic acid (B_5)	1.3 mg		
Vit B_6	0.40 mg		
Folic acid	64 μg		
Vit B_{12}	0.70 μg		
Biotin	9.6 μg		
Vit C	24 mg		

Table 2 Social and demographic characteristics of patients before surgery.

		Group 1	Group 2
		N = 52	N = 52
Gender	male	27 (51.92%)	29 (55.77%)
	female	25 (48.08%)	23 (44.23%)
Aggregated age	average	57.46 SD ±7.92, median 57	57.92 SD ±8.27, median 58
Marital status	married	30 (57.69%)	28 (53.85%)
	divorced	5 (9.61%)	7 (13.46%)
	widower / widow	12 (23.07%)	11 (21.15%)
	single	5 (9.61%)	6 (11.53%)
Degree of education	analphabet	0	0
	High school	38 (73.07%)	42 (80.76%)
	University	11 (21.15%)	10 (19.23%)
	postgraduate	3 (5.76%)	0

Metastases occurred in the first group in 20 patients, representing 38.46% and in the control group in 7 patients (13.46%). 73.07% of patients had the mild systemic disease before surgery, 13.46% had a severe one and 13.46% were without systemic disease in the first group. In the control group, before surgery, 80.76% had mild systemic disease, representing 42 patients, three patients had severe systemic disease, representing 5.76%, and 7 patients had no systemic disease, representing 13.46%. The average height of the whole group of patients was 1.60 ±9.09 meters, weight 71.6 ±11.64 kilograms a month before surgery, and 71 ±12.61 kilograms just before surgery. The average weight in the first group of patients one month before surgery was 72 ±7.45 kilograms, just before surgery 73 ±12.85 kilograms and in the second group 71.9 ±10.87 kilograms a month before surgery and 71.5 ±9.64 kilograms just before surgery.

Laboratory variables

Laboratory variables are shown in Table 4. Changes in variables were reported, that means laboratory parameters of haemoglobin, leukocytes, albumin, total proteins, CRP, glycaemia in patients in initial state with enteral nutrition and just prior to surgical procedures, and then compared with the control group.

Table 3 Clinical characteristics of patient before surgery.

		Treatment group	Control group
Onset of illness in months	0 – 3	5 (9.61%)	11 (21.15%)
	4 – 6	30 (57.69%)	6 (11.53%)
	7 – 12	12 (23.07%)	28 (53.85)
	>13	5 (9.61%)	7 (13.46%)
stage	I.	10 (19.23%)	7 (13.46%)
	II.	25 (48.07%)	10 (19.23%)
	III.	7 (13.46%)	25 (48.07%)
	IV.	10 (19.23%)	10 (19.23%)
metastasis	no	32 (61.53%)	45 (86.53%)
	yes	20 (38.46%)	7 (13.46%)
comorbidity	mild systemic disease	38 (73.07%)	42 (80.76%)
	severe systemic disease	7 (13.46%)	3 (5.76%)
	without systemic disease	7 (13.46%)	7 (13.46%)

Table 4 Laboratory variables.

		Treatment group		
	Reference value	**Initial status**	**Status just before surgery**	***p*-value**
Haemoglobin Hb ($g.L^{-1}$)	Male (130 – 197) /Female (120 – 160)	114.2 ±18.04	116.90 ±16.26	0.0168
Leukocytes WBC ($10^9.L^{-1}$)	3.8.2010	8.72 ±3.6	7.74 ±3.168	0.0025
Albumin S-ALB ($g.L^{-1}$)	32 – 48	35.42 ±6.92	37.48 ±6.38	0.0008
Total proteins S-CB ($g.L^{-1}$)	57 – 82	56.02 ±6.43	61.1 ±8.7	0.0002
CRP-C reactive protein ($mg.L^{-1}$)	0 – 5	26.5 ±35.00	14.092 ±15.38	0.0007
Glycemia S-Glu ($mmol.L^{-1}$)	4.0 – 5.5	7.3 ±2.93	6.87 ±2.21	0.0153

Table 5 Postoperative complications.

	Treatment group	Control group	*p*-value
Septic complications	4%	25%	0.04
Total complications	21%	29%	0.51

In patients receiving enteral nutrition, the albumin and total proteins increased, which was statistically significant and there was a decrease in the number of leukocytes and CRP, statistically significant, and also glycemia was adjusted. In the treatment group, the haemoglobin changed from 114.2 to 116.90, $p = 0.0168$, leukocytes WBC from 8.72 to 7.74, $p = 0.0025$, albumin S-ALB from 35.42 to 37.48, $p = 0.0008$, total proteins S-CB from 56.02 to 61.1, $p = 0.0002$, CRP-C reactive protein from 26.5 to 14.092, $p = 0.0007$, glycemia S-Glu from 7.3 to 6.87, $p = 0.0153$. In the control group, the haemoglobin changed from 113.0 to 115.61, $p = 0.0097$, leukocytes WBC from 8.25 to 7.98, $p = 0.0973$, albumin S-ALB from 33.15 to 33.57, $p = 0.1073$, total proteins S-CB from 57.1 to 58.94, $p = 0.00108$, CRP-C reactive protein from 10.6 to 10.45, $p = 0.247$, glycaemia S-Glu from 6.31 to 5.85, $p = 0.027$. In the control group, there was a change in total protein, which was statistically significant.

Postoperative complications

Postoperative complications within 30 days are listed in Table 5. The number of septic complications was significantly lower in patients in the treatment group with enteral nutrition than in patients in the control group (4% compared to 25%, $p = 0.04$). There wasn´t a significant difference in the number of total complications between the two groups (21% compared to 29%, $p = 0.51$).

This study retrospectively examined the association of laboratory parameters, namely albumin, total proteins, leukocytes, CRP, glycemia, and preoperative enteral nutrition in patients who underwent a resection of the colon for malignancies. In our study, we reported adding Nutridrink to patients with the oncological disease for at least 21 days, which increased serum albumin, total proteins, and reduced CRP levels in patients undergoing planned colon resection. This preoperative preparation can be a useful strategy as a preoperative method to improve postoperative forecasts in patients. The systemic score of

inflammation and nutrition plays an important role in various cancers in certain situations. The reports have shown that inflammation promotes the invasion of tumors and metastases through the activation of IL-6 and T-lymfocytes **(Tokunaga et al., 2017)**. Our study showed that the addition of Nutridrink to treatment before surgery reduced CRP levels and increased serum albumin of total proteins in patients with colorectal cancer who had undergone a therapeutic resection of the colon. We believe that our result is remarkable because our two groups have been well aligned with respect to the basic demographic parameters, thus reducing confusing variables. The surgical variability was reduced because the surgical procedure was performed by one surgeon in both groups.

There are some limitations to this study. Firstly, our set of patients was small, second, nutrition disorders in cancer patients occur not only by cancer pathologies but also by preoperative chemotherapy or radiotherapy, thirdly, our study was retrospective and was performed on one institution. Nevertheless, it is a study, which in Slovakia is one of few comparing the effect of enteral preoperative nutrition in a patient with colorectal cancer undergoing surgical resection. Serum albumin levels are traditionally used as a biochemical indicator of individual nutritional status before surgery. It is considered to be the exact preoperative prognostic indicator for various surgical performances including cardiac, trauma, and general surgery **(Truong et al., 2016)**. While some believe that low albumin levels indicate malnutrition, others assume that hypoalbuminemia stems from a state of chronic disease, and this a resulting inflammation and is not caused by malnutrition, thereby preventing any beneficial effects of nutritional therapy **(Truong et al., 2016)**. With respect to serum albumin levels, this value gradually decreases between 0.08 and 0.17 $g.l^{-1}$ per year with age. In addition, elderly patients are usually complicated by comorbidities that increase inflammatory cytokines, and both loss of appetite and loss of muscle mass directly cause hypoalbuminemia **(Tominaga et al. 2019)**.

However, enteral and parenteral nutrition have been shown to improve the results in undernourished patients undergoing large elective surgical intervention **(Braga et al., 2002)**. The agreement is to stabilize the baseline nutritional status and administer the enteral or parenteral nutrition to the severely hypoalbuminate patients before surgery, even if it requires the delay of surgery. In 2012, **Oberhofer et al. (2012)** showed an increase in CRP in the early postoperative period after colorectal tract surgery correlated with a significant increase in complication rates (p <0.001), which was consistent with Welsch **(Welsch et al., 2007)**, who showed that CRP values greater than 140 $mg.l^{-1}$ on a postoperative day 3 or 4 predicted infectious complications and anastomotic leaks after colorectal surgery. In contrast, preoperative CRP levels did not correlate with the incidence of postoperative complications **(Truong et al., 2016)**. CRP is an acute-phase protein that is synthesized in the liver in response to proinflammatory cytokine signaling, primarily through interleukin-6 and alpha tumor necrosis factor. An important role of CRP is to bind phosphocholine to pathogens as well as to apoptotic or necrotic host cells, which in turn activate the complement system and obtain phagocytes.

Serum CRP increases rapidly in response to tissue damage or infection, but an increase in CRP (generally at low levels) is also seen in chronic inflammatory or neoplastic conditions, a process likely to be mediated by various signaling mechanisms **(Crockett et al., 2014)**. **Platt et al. (2012)** reported data on WBC, CRP, and albumin concentrations in 454 patients undergoing colorectal cancer surgery, of which 104 developed infectious complications. The results showed that CRP measurements after resection for colorectal carcinoma accurately predict infectious complications including anastomotic leakage.

The average time to onset of infectious complications, including anastomotic leakage, was 6 – 8 days after surgery. Colorectal surgery has traditionally been associated with significant morbidity and prolonged hospital stay. The overall complication rate was reported to be 26 – 35%. In particular, infectious complications are a major cause of morbidity and mortality after colorectal surgery **(Sonoda et al., 2015)**. Albumin is considered a negative protein in the acute phase because its concentration decreases during injury and sepsis. In patients with septic shock, the rate of albumin loss in tissue spaces increases by more than 300%. Hypoalbuminaemia is a risk factor for mortality and postoperative complications. Therefore, nutrition control is an important focus of perioperative management. The magnitude of the systemic inflammatory response during the perioperative period, as indicated by acute-phase proteins – in particular C-reactive protein (CRP) – can help identify the risk of postoperative infectious complications.

A correlation was reported between serum albumin and CRP with gastrointestinal cancer **(Feng, Zhao and Chen, 2014)**.

Anastomosis leakage after rectal surgery is one of the most serious and life-threatening complications and still poses a main clinical problem **(Welsch et al., 2007)**. Up to 50% of patients with anastomotic leakage are asymptomatic, which can be explained by extraperitoneal localization of leakage. Postoperative mortality on anastomotic complications is up to 22% and it is estimated, that it constitutes one-third of all deaths after colorectal surgery **(Nesbakken et al., 2005)**. New recommendations for operations and oncology were published in 2016 and 2017. Nutritional intervention before major surgery in patients with malnutrition should be made for at least 10 – 14 days, even at the cost of defering the operation (at least 7 – 14 days) and this is a strong recommendation. Enteral nutrition is the preferred way of feeding. Parenteral nutrition is recommended only if the patient cannot be fed through the digestive tract **(Weimann et al., 2017; Arends et al., 2017)**. However, enteral and parenteral nutrition has been shown to improve the results in undernourished patients undergoing large elective surgical intervention **(Braga et al., 2002)**. Undoubtedly the use of enteral nutrition reduces the number of perioperative complications and decreases the time spent in the hospital **(Heyland et al., 2001)**. It should be remembered that it is very important to continue the nutritional intervention even after the operation **(Klek et al., 2011)**. For example, Giger-Pabst **(Giger-Pabst et al., 2013)**, found that preoperative peroral supplementation

with an immune-enriched diet for 3 days did not improve postoperative outcome in patients with gastrointestinal cancer and meanwhile, no positive effects of immunonutritional support were found in patients on ICU. **(Atkinson, Sieffert and Bihari, 1998; Bower et al., 1995)**. The study, which included 1223 critically ill adults, also showed the deleterious effect of early immunonutritional administration **(Heyland et al., 2013)**. In the past, the originally popular parenteral nutrition was replaced by enteral feeding in the early 1990s. Many experts have supported changes in the nutritional approach, especially because there is a lack of evidence-based data. Few authors dared to express their doubts about the enteral technique, including difficulties in administering the required dose or the occurrence of complications **(Braga et al., 1999; Gianotti et al., 2000; Gianotti et al., 2002; Gianotti et al., 1997; Heslin et al., 1997; Klek et al., 2008)**. The management of malnutrition in patients with metastatic carcinoma belongs to the complex management of illness, so the tolerance and effectiveness of ever more aggressive treatment increases and the life quality of patients improve as well **(Gallois et al., 2019)**.

CONCLUSION

In conclusion, our study shows that albumin, total protein, CRP may be a useful marker in colorectal cancer patients suffering from malnutrition. In addition, further extensive studies are needed to evaluate the clinical utility of enteral preoperative nutrition and nutritional markers.

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Contact address:

MUDr. Mária Servátková, Slovak University of Agriculture in Nitra, Department of Human Nutrition, Faculty of Agrobiology and Food Resources, Tr. A. Hlinku 2, 949 76 Nitra, Tel.: +421902182395,
E-mail: maria.servatkova@gmail.com
ORCID: https://orcid.org/0000-0002-4222-784X

MUDr. Peter Chlebo, PhD., Slovak University of Agriculture in Nitra, Department of Human Nutrition, Faculty of Agrobiology and Food Resources, Tr. A. Hlinku 2, 949 76 Nitra, Tel.: +421376414883,
E-mail: Peter.Chlebo@uniag.sk
ORCID: https://orcid.org/0000-0002-3897-2169

Ing. Zuzana Chlebová, PhD., Slovak University of Agriculture in Nitra, Department of Human Nutrition, Faculty of Agrobiology and Food Resources, Tr. A. Hlinku 2, 949 76 Nitra, Tel.: +421376414880,
E-mail: Zuzana.Chlebova@uniag.sk
ORCID: https://orcid.org/0000-0002-4145-8187

Corresponding author: *