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Perioperative Enteral Supplementation and Early Postoperative Changes in Serum Proteins and Inflammatory Markers Following Colorectal Cancer Resection

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Abstract

Background: The early postoperative period following colorectal cancer resection is characterized by metabolic stress, protein catabolism, and systemic inflammation. Although perioperative nutritional support is increasingly recognized as an important component of surgical care, its relationship with short-term changes in serum proteins and inflammatory markers has been less extensively investigated.

Methods: This prospective, comparative study included 60 adults undergoing elective open colorectal cancer resection with primary anastomosis. The supplementation group included 30 patients who received 300 mL/day of an enteral nutritional formula for two days before and seven days after surgery, with postoperative supplementation initiated 24 hours after the procedure. Standard nutritional care without enteral supplementation was provided to the remaining 30 patients. Serum total protein, albumin, C-reactive protein (CRP), and fibrinogen were assessed preoperatively and on postoperative days (PODs) 3, 5, and 7. Early postoperative morbidity was evaluated within seven days.

Results: Baseline total protein, erythrocyte count, and fibrinogen were higher in the supplementation group. From baseline to POD7, mean decreases in total protein (5.07 ± 4.43 vs 9.57 ± 2.65 g/L; $t(58) = 4.77$, $p < 0.001$) and albumin (5.20 ± 4.37 vs 9.37 ± 2.74 g/L; $t(58) = 4.43$, $p < 0.001$) were smaller in the supplementation group. Mean increases in CRP (18.02 ± 18.55 vs 36.59 ± 27.87 mg/L; $t(58) = -3.04$, $p = 0.004$) and fibrinogen (0.97 ± 0.85 vs 2.67 ± 0.60 g/L; $t(58) = -8.95$, $p < 0.001$) were also smaller. Early postoperative complications occurred in two of 30 patients in the supplementation group and five of 30 patients in the standard-care group. No in-hospital deaths occurred.

Conclusion: Perioperative enteral supplementation was associated with smaller early postoperative decreases in serum total protein and albumin and smaller increases in CRP and fibrinogen following colorectal cancer resection. The clinical significance of these biochemical differences remains uncertain, and the comparison of early postoperative morbidity was inconclusive. Given the study design and baseline imbalances, the findings warrant confirmation in larger, adequately controlled studies.

Categories: Nutrition, General Surgery, Oncology

Keywords: colorectal cancer (crc), colorectal resection, enteral nutrition, inflammatory markers, perioperative nutrition

Introduction

Colorectal cancer remains one of the most commonly diagnosed malignancies and the second leading cause of cancer-related death worldwide [1]. Although incidence patterns vary across countries and age groups, recent population-based data indicate an increasing incidence of colorectal cancer among adults younger than 50 years in many regions [2]. Despite advances in multimodal oncological treatment, surgical resection remains the cornerstone of potentially curative treatment for localized disease [3]. However, major colorectal surgery is associated with considerable metabolic stress, systemic inflammation, and postoperative catabolism, which may delay recovery and increase the risk of postoperative complications [4].

Malnutrition and nutritional risk are common among patients with colorectal cancer and are associated with higher postoperative morbidity, impaired wound healing, prolonged hospitalization, and poorer prognosis [5]. Traditional postoperative fasting was historically intended to reduce the risk of nausea, aspiration, ileus, and anastomotic complications. However, accumulating evidence has challenged this approach, indicating that early oral or enteral feeding is generally safe and may support recovery after colorectal surgery [6,7]. Modern perioperative care and enhanced recovery after surgery protocols emphasize the early resumption of oral feeding and the early initiation of nutritional therapy, particularly in patients at nutritional risk [8].

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In addition to the timing of perioperative nutritional support, adequate energy and protein intake is equally important during postoperative recovery. Nutritional supplementation may help patients meet these requirements during the period of increased metabolic demand after surgery. However, its effects may depend on patients' baseline nutritional status and on the composition, dose, and duration of supplementation [8,9]. Previous studies have mainly focused on postoperative complications and length of hospital stay, whereas short-term changes in routine laboratory markers of inflammation and nutritional status during the first postoperative week remain less well characterized [9,10]. Assessing these markers at several time points may provide a clearer picture of how they change during the first postoperative week.

The aim of this study was therefore to compare postoperative changes in selected inflammatory and laboratory nutritional markers between patients receiving perioperative enteral nutritional supplementation and those receiving standard nutritional care following elective open colorectal cancer resection. Changes were assessed from the preoperative period through postoperative days (PODs) 3, 5, and 7. Postoperative morbidity during the early recovery period was examined as a secondary outcome. We hypothesized that perioperative nutritional supplementation would be associated with an attenuated postoperative inflammatory response and smaller reductions in selected laboratory nutritional markers.

Materials And Methods

Study design and setting

This single-center, prospective comparative study was conducted at the Department of Colorectal Surgery, Clinic of Surgery, University Clinical Center Tuzla, Bosnia and Herzegovina, between June 2014 and December 2015. The study involved adult patients undergoing elective open colorectal resection with primary anastomosis for colorectal cancer. The original study was approved by the Ethics Committee of University Clinical Center Tuzla (No. 02-09/2-60/14). The same committee subsequently authorized publication of the study results (No. 02-09/2-102/26). All participants provided informed consent before enrollment.

Participants

Patients were eligible if they were 18 years of age or older and underwent elective open colorectal resection with primary anastomosis for histologically confirmed colorectal cancer. Exclusion criteria were intolerance or allergy to the enteral formula, impaired mental status, planned multivisceral resection, incomplete medical documentation, and refusal to participate. The study population comprised 60 patients divided into two groups according to perioperative nutritional management: 30 patients received perioperative enteral nutritional supplementation, while 30 received standard nutritional care without enteral supplementation.

Perioperative management

All patients were managed within the same colorectal surgical unit according to institutional perioperative protocols. These protocols included antibiotic prophylaxis, thromboprophylaxis with low-molecular-weight heparin, postoperative analgesia, mobilization, and standardized postoperative oral feeding in both groups. Surgical procedures were performed according to established oncological principles for colorectal cancer surgery [11].

Nutritional intervention

Patients in the supplementation group ($n = 30$) received 300 mL/day of a ready-to-use enteral nutritional formula (Fresubin®, Fresenius Kabi, Germany) for two consecutive preoperative days and seven consecutive PODs. The formula provided 150 kcal, 10 g of protein, 12.4 g of carbohydrates, and 6.7 g of fat per 100 mL, together with vitamins and minerals. At the prescribed volume of 300 mL/day, this corresponded to a daily contribution of 450 kcal and 30 g of protein. Postoperative supplementation was initiated orally 24 hours after surgery and divided into approximately 50 mL portions administered every four hours. The timing of postoperative supplementation was consistent with the 24-hour window used to define early enteral feeding in previous colorectal surgery research [12]. The supplement was provided in addition to routine perioperative nutritional care. Patients in the control group ($n = 30$) received routine perioperative nutritional care without the study supplement.

Data collection and outcome measures

Demographic data, including age and sex, were obtained from patients' medical records. Anthropometric and laboratory assessments were performed preoperatively and on PODs 3, 5, and 7. Baseline laboratory and anthropometric assessments were performed before the initiation of preoperative nutritional supplementation and served as the reference values for evaluating postoperative changes. Body mass index (BMI) was calculated as body weight in kilograms divided by height in meters squared. Anthropometric measurements were performed using the same calibrated equipment under standardized conditions on the surgical ward, with no missing or estimated values. Laboratory assessments included serum total protein, albumin, erythrocyte count, and hemoglobin. Inflammatory markers included C-reactive protein (CRP), total leukocyte count, neutrophil percentage, and fibrinogen. The main outcomes of interest were changes in

serum total protein, albumin, CRP, and fibrinogen during the first postoperative week, with particular attention to between-group differences in changes from baseline to POD7. Early postoperative morbidity was evaluated as a secondary outcome and was defined as the occurrence of at least one documented abdominal or extra-abdominal postoperative complication within the first seven days after surgery, as identified from the clinical records. In-hospital mortality was recorded separately and reported descriptively.

Statistical analysis

Continuous variables were summarized as means and standard deviations (SDs), and categorical variables were summarized as frequencies and percentages. Between-group differences in continuous variables at the preoperative assessment and on PODs 3, 5, and 7 were evaluated using independent-samples Student's *t*-tests. Changes from the preoperative assessment to POD7 were defined as the POD7 value minus the corresponding preoperative value and were compared between groups using the same test. Between-group mean differences in changes from baseline to POD7 were reported with 95% confidence intervals (CIs) calculated using the pooled-variance Student's *t*-test. Statistical calculations were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY). Categorical outcomes were compared using Fisher's exact test. The risk ratio (RR) for early postoperative morbidity was calculated relative to the control group, and its 95% CI was estimated using the log-Wald method. All tests were two-sided, with *p* < 0.05 considered statistically significant. Analyses were unadjusted for potential confounders, and no correction for multiple comparisons was applied. The findings were therefore interpreted as exploratory.

Results

A total of 60 patients undergoing elective colorectal cancer surgery were included, with 30 patients in each study group. Mean age did not differ significantly between the supplementation and control groups (63.6 ± 8.7 vs 64.3 ± 9.3 years; *p* = 0.76), and the sex distribution was identical, with 17 men and 13 women in each. At baseline, BMI, albumin, hemoglobin, CRP, total leukocyte count, and neutrophil percentage did not differ significantly between the groups. However, total protein, erythrocyte count, and fibrinogen were significantly higher in the supplementation group (*p* = 0.005, *p* = 0.018, and *p* = 0.029, respectively; Table 1).

Variable	Supplementation group (n = 30)	Control group (n = 30)	Test statistic	p-value
Male sex, n (%)	17 (56.7)	17 (56.7)	Fisher's exact test	1.000
BMI (kg/m ²)	25.94 ± 3.32	25.41 ± 2.28	<i>t</i> = 0.72	0.474
Total protein (g/L)	67.33 ± 4.56	64.23 ± 3.50	<i>t</i> = 2.95	0.005*
Albumin (g/L)	39.70 ± 3.49	38.13 ± 2.54	<i>t</i> = 1.99	0.051
RBC (×10 ¹² /L)	4.18 ± 0.26	4.01 ± 0.28	<i>t</i> = 2.44	0.018
Hemoglobin (g/L)	123.90 ± 8.34	124.30 ± 5.48	<i>t</i> = -0.22	0.827
CRP (mg/L)	4.26 ± 3.31	4.46 ± 2.78	<i>t</i> = -0.25	0.801
WBC (×10 ⁹ /L)	6.45 ± 0.81	6.40 ± 0.56	<i>t</i> = 0.28	0.782
Neutrophils (%)	58.37 ± 2.62	57.23 ± 2.30	<i>t</i> = 1.79	0.079
Fibrinogen (g/L)	3.38 ± 0.44	3.15 ± 0.35	<i>t</i> = 2.24	0.029

TABLE 1: Baseline characteristics and laboratory values according to study group

Data are presented as mean ± SD unless otherwise indicated. Between-group comparisons of continuous variables were performed using two-sided independent-samples Student's *t*-tests (*df* = 58). Sex distribution was compared using Fisher's exact test. Reported *p*-values are unadjusted for multiple comparisons.

BMI, Body mass index; CRP, C-reactive protein; RBC, Red blood cells; WBC, White blood cells.

Postoperative changes in total protein and albumin followed a similar overall pattern in both groups, with higher concentrations in the supplementation group throughout follow-up. Following the initial decline, serum protein concentrations partially recovered by POD7 but remained below preoperative levels, with albumin still higher in the supplementation group (34.50 vs 28.77 g/L; *t*(58) = 6.52, *p* < 0.001). This recovery coincided with declining inflammatory marker levels toward the end of the first postoperative week. CRP reached its highest measured concentrations on POD5 before declining in both groups, with lower levels in the supplementation group on POD7 (22.28 vs 41.06 mg/L; *t*(58) = -3.03, *p* = 0.004). Fibrinogen declined

across successive postoperative assessments and remained consistently lower in the supplementation group. Despite these declines, mean CRP and fibrinogen concentrations remained above their preoperative values at the end of the observation period (Table 2).

Parameter	POD	Supplementation group (n = 30)	Control group (n = 30)	t statistic	p-value
Total protein (g/L)	3	57.70 ± 4.91	53.07 ± 3.55	4.19	<0.001
	5	58.90 ± 4.24	53.03 ± 3.48	5.86	<0.001
	7	62.27 ± 5.35	54.67 ± 4.06	6.20	<0.001
Albumin (g/L)	3	30.13 ± 3.93	27.03 ± 2.88	3.48	<0.001
	5	31.03 ± 3.01	26.77 ± 3.19	5.32	<0.001
	7	34.50 ± 3.42	28.77 ± 3.39	6.52	<0.001
Hemoglobin (g/L)	3	111.57 ± 7.15	107.00 ± 6.63	2.57	0.013
	5	112.40 ± 7.41	107.77 ± 7.16	2.46	0.017
	7	117.43 ± 7.76	112.13 ± 7.33	2.72	0.009
RBC (×10 ¹² /L)	3	3.75 ± 0.38	3.35 ± 0.61	3.05	0.003
	5	3.77 ± 0.33	3.38 ± 0.61	3.08	0.003
	7	3.87 ± 0.39	3.42 ± 0.62	3.37	0.001
BMI (kg/m ²)	3	24.37 ± 3.22	23.42 ± 2.12	1.35	0.182
	5	24.75 ± 3.27	23.54 ± 2.13	1.70	0.095
	7	25.24 ± 3.28	23.69 ± 2.20	2.15	0.036
CRP (mg/L)	3	54.21 ± 16.75	48.83 ± 11.76	1.44	0.155
	5	74.93 ± 24.32	78.79 ± 36.14	-0.49	0.629
	7	22.28 ± 19.31	41.06 ± 27.90	-3.03	0.004
WBC (×10 ⁹ /L)	3	12.75 ± 2.30	13.41 ± 2.22	-1.13	0.263
	5	8.45 ± 1.77	9.58 ± 2.36	-2.10	0.040
	7	7.14 ± 1.24	8.23 ± 1.83	-2.70	0.009
Neutrophils (%)	3	73.23 ± 3.82	73.80 ± 4.12	-0.56	0.581
	5	64.60 ± 2.81	67.60 ± 5.04	-2.85	0.006
	7	60.93 ± 3.35	62.70 ± 3.94	-1.87	0.066
Fibrinogen (g/L)	3	5.57 ± 0.89	6.65 ± 0.63	-5.42	<0.001
	5	5.09 ± 0.96	6.33 ± 0.59	-6.03	<0.001
	7	4.35 ± 0.95	5.82 ± 0.58	-7.23	<0.001

TABLE 2: Anthropometric and laboratory measures on postoperative days 3, 5, and 7

Data are presented as mean ± SD. Between-group comparisons were performed using two-sided independent-samples Student's t-tests (df = 58). Reported p-values are unadjusted for multiple comparisons.

BMI, Body mass index; CRP, C-reactive protein; POD, Postoperative day; RBC, Red blood cells; WBC, White blood cells.

The comparison of baseline-to-POD7 changes showed smaller declines in serum proteins in the supplementation group. Between-group differences in mean change were 4.50 g/L for total protein and 4.17 g/L for albumin ($t(58) = 4.77$ and 4.43 , respectively; both $p < 0.001$). Smaller increases in CRP and fibrinogen were also observed, with the mean increase in CRP being approximately half that in the control group (18.02 vs 36.59 mg/L; $t(58) = -3.04$, $p = 0.004$; Table 3).

Parameter	Supplementation group (n = 30)	Control group (n = 30)	Between-group difference (95% CI)	t statistic	p-value
Total protein (g/L)	-5.07 ± 4.43	-9.57 ± 2.65	4.50 (2.61 to 6.39)	4.77	<0.001
Albumin (g/L)	-5.20 ± 4.37	-9.37 ± 2.74	4.17 (2.29 to 6.05)	4.43	<0.001
CRP (mg/L)	+18.02 ± 18.55	+36.59 ± 27.87	-18.57 (-30.80 to -6.34)	-3.04	0.004
Fibrinogen (g/L)	+0.97 ± 0.85	+2.67 ± 0.60	-1.70 (-2.08 to -1.32)	-8.95	<0.001

TABLE 3: Changes in the main laboratory outcomes from baseline to postoperative day 7

Data are presented as mean change ± SD (POD7 minus baseline). Negative and positive values indicate decreases and increases, respectively. Between-group comparisons were performed using two-sided independent-samples Student's t-tests (df = 58). Between-group mean differences are presented with 95% confidence intervals. Reported p-values are unadjusted for multiple comparisons.

CRP, C-reactive protein; POD, Postoperative day.

At least one early postoperative complication occurred in seven of 60 patients (11.7%): two of 30 (6.7%) patients in the supplementation group and five of 30 (16.7%) patients in the control group. The between-group difference was not statistically significant (RR, 0.40; 95% CI, 0.08-1.90; Fisher's exact p = 0.42). The wide CI indicates considerable uncertainty in the estimated RR for early postoperative morbidity. No in-hospital deaths occurred.

Discussion

The principal finding of our study was that perioperative enteral nutritional supplementation was associated with smaller changes in selected nutritional and inflammatory markers during the first week after elective open colorectal cancer surgery. Compared with the control group, patients receiving supplementation showed less pronounced reductions in serum total protein and albumin and smaller increases in CRP and fibrinogen from baseline to POD7. Early postoperative morbidity did not differ significantly between the groups, although the number of recorded complications was small.

The postoperative decline in serum albumin and total protein observed in both groups is a well-recognized response to major surgery. Although both parameters are routinely used in nutritional assessment, their early postoperative course is also influenced by the surgical stress response. Albumin, in particular, is a negative acute-phase protein, and its rapid decline may reflect redistribution into the interstitial compartment, hemodilution, altered hepatic synthesis, and increased catabolism [13]. Previous prospective studies have shown that the magnitude of postoperative albumin decline is related to surgical stress and the inflammatory response [14,15]. The smaller decreases in albumin and total protein among patients receiving supplementation could therefore reflect a less pronounced metabolic and inflammatory disturbance, although these changes alone do not demonstrate improved nutritional status. CRP increased in both groups, consistent with the acute-phase response following colorectal resection [15]. The highest measured mean concentrations were recorded on POD5. Values did not differ significantly between the groups on POD3 or POD5 but were lower in the supplementation group on POD7. The lower CRP concentration observed on POD7 should be regarded as an exploratory finding and does not establish more rapid resolution of inflammation or differences in postoperative inflammatory trajectories. Despite being slightly higher at baseline, fibrinogen showed a smaller increase by POD7 and was lower in the supplementation group at each postoperative assessment. These observations suggest differences in the postoperative inflammatory course, but both markers are nonspecific and may be influenced by the extent of surgery, perioperative fluid shifts, infection, and other postoperative complications [16,17].

The distinction between biochemical changes and clinical outcomes is also evident in previous studies, although differences in nutritional protocols limit direct comparisons. Ural et al. reported more favorable postoperative changes in albumin and CRP when immunonutrition was continued after colorectal cancer surgery but found no statistically significant differences in hospital stay or postoperative complications [18]. In the SONVI trial, perioperative immunonutrition within an ERAS (Enhanced Recovery After Surgery) pathway was associated with fewer overall and infectious complications, particularly wound infections, than standard oral nutritional supplementation, while length of hospital stay was similar between the groups [19]. A recent systematic review and meta-analysis showed a similarly mixed pattern, with fewer minor infectious complications but no significant differences in major infectious or noninfectious complications or length of hospital stay [20]. However, these studies primarily evaluated immunonutrition, whereas the present study examined standard nutritional supplementation compared with routine care without the study supplement. Differences in supplement composition and comparator groups limit direct comparisons, and

findings from immunonutrition studies should therefore be considered contextual rather than direct evidence supporting our observations. In our cohort, the clinical significance of the observed biochemical differences remains uncertain, and the comparison of early postoperative morbidity was inconclusive.

Current perioperative guidelines emphasize the early resumption of oral or enteral nutrition and individualized nutritional support when usual intake is expected to be insufficient [8]. Accordingly, the relevance of our findings lies less in the early initiation of enteral intake itself than in the potential value of providing additional nutritional support throughout the perioperative period. In our cohort, supplementation was associated with a more favorable early postoperative biochemical course; however, these laboratory differences should be interpreted alongside clinical outcomes rather than as evidence of clinical benefit. The strengths of this study include its prospective design, serial laboratory assessments at standardized postoperative time points, and management of both groups within the same colorectal surgical unit. Several limitations should be acknowledged. The study design and baseline differences in total protein and fibrinogen may have influenced the observed postoperative patterns. Although change-score analyses focused on differences from baseline, they could not eliminate the influence of these imbalances. Detailed group-level data on tumor location and stage, type of resection, comorbidity burden, and baseline nutritional risk were unavailable, precluding evaluation and adjustment for other clinically relevant differences between the groups. The nutritional supplementation protocol provided a defined energy and protein contribution, although individual variations in dietary intake and perioperative fluid balance may have influenced the observed postoperative changes. The substantial early postoperative changes in BMI should also be interpreted cautiously, as perioperative fluid shifts may have influenced body weight measurements and may not reflect actual changes in nutritional status. The small sample and limited number of complications reduced the precision of the clinical estimates. The timing and severity of individual postoperative complications were not available for further analysis, limiting assessment of their potential influence on subsequent laboratory measurements. Analyses were unadjusted for potential confounders and did not include longitudinal modeling; multiple comparisons without correction for multiplicity increased the possibility of chance findings. Postoperative laboratory assessments and evaluation of morbidity were limited to the first seven days after surgery. The evaluated biomarkers are also nonspecific and influenced by the surgical inflammatory response and fluid shifts. Finally, the single-center setting and changes in colorectal surgical and nutritional practice since data collection may limit the applicability of these findings to contemporary perioperative care.

Conclusions

Perioperative enteral nutritional supplementation was associated with smaller decreases in serum total protein and albumin and smaller increases in CRP and fibrinogen from baseline to POD7 following elective open colorectal cancer surgery. The clinical significance of these observed biochemical differences remains uncertain. The comparison of seven-day postoperative morbidity was inconclusive due to the small number of complications and wide CI. Given the study design and baseline imbalances, these associations should not be interpreted as evidence of a causal treatment effect. Larger, adequately powered randomized studies with clearly defined nutritional exposure and appropriate control of baseline differences are needed to determine whether these biochemical differences translate into clinically meaningful benefits.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Ethics Committee of the University Clinical Center Tuzla, Bosnia and Herzegovina, issued approval (No. 02-09/2-60/14). **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform

disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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