The Effect of Preoperative Enteral Immunonutrition on Surgical Results and Cost in Patients with Rectal Tumors Who Underwent Low Anterior Resection Without Diverting Ostomy

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Article

The Effect of Preoperative Enteral Immunonutrition on Surgical Results and Cost in Patients with Rectal Tumors Who Underwent Low Anterior Resection Without Diverting Ostomy

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Abstract: Background: Immune modulating enteral nutrition in the preoperative period may reduce postoperative complications in cancer patients. The aim of the study is to evaluate the effect of immune modulating enteral nutrition on postoperative complications in patients who received neoadjuvant chemo-radiotherapy for rectal tumor and subsequently underwent low anterior resection without diverting ostomy. **Methods:** Preoperative immunonutrition (arginine, omega 3 fatty acids and dietary nucleotides) versus standard nutrition was evaluated. Mortality, infective complications in the first 30 days after the operation, length of hospital stay, cost analysis and laboratory results were analyzed. **Results:** There was no statistically significant difference between the IN-given and standard-fed groups in terms of postoperative complications, including urinary system (p=1.000) and wound infection (p=0.194), intraabdominal abscess (p=0.493), pulmonary complications (p=0.734), venous thromboembolism (p=1.000), ileus (p=1.000), and anastomotic leak (p=614)). However, the hospital stay was shorter (p=0.022) and the total cost (p=0.013) was lower in the immunonutrition group. **Conclusion:** Immunonutrition has the potential to reduce the length of hospital stay and hospital costs for patients undergoing surgery for locally advanced rectal cancer.

Keywords: immunonutrition; rectal cancer; complications; low anterior resection; chemoradiotherapy

1. Introduction

Enteral immunonutrient formulas, including arginine, nucleotides, and long-chain n-3 fatty acids, are widely used in surgical patients [1]. In many studies, it has been shown that the preoperative administration of these mixtures above physiological doses to patients undergoing gastrointestinal surgery reduces the postoperative complication rates and shortens the length of hospital stay [2–5]. This benefit has also been demonstrated in patients without malnutrition risk [6]. In the ESPEN guidelines, the use of immune modulating formulas in patients undergoing abdominal cancer surgery and at risk of significant malnutrition is recommended [7].

Colorectal cancers are one of the most frequently diagnosed cancers in the world, with an annual incidence of 73.2/100,000 according to GLOBACON in 2022 [8]. Despite advances in surgical technique and patient care, infectious complications, anastomotic and wound site problems remain a major challenge following colon surgery. Especially infective complications increase hospital costs significantly. [9]. Rectal cancer patients preparing for surgery are exposed to the physiologic stress of chemotherapy and radiotherapy as neoadjuvant treatment in the preoperative period. The adverse

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effects of oncologic treatment on nutrition, poor nutrient intake, and increased nutrient requirements may negatively affect postoperative patient outcomes.

Although there are data on immune nutrition in patients with colorectal cancer, results collected in patients with isolated rectal cancer are still lacking. Furthermore, the impact of enteral immunonutrition (IN) on patients with rectal cancer who received neoadjuvant chemoradiotherapy in the preoperative period is not yet clear. The aim of this study was to compare the surgical outcomes in patients with rectal tumors receiving neoadjuvant chemoradiotherapy (CRT) between patients who received a standard oral nutrition regimen and those who received preoperative support using an immune modulating formula.

2. Materials and Methods

Patient Selection: The inclusion criteria for this study are as follows: (i) patients diagnosed with rectal tumor and receiving long-term CRT preoperatively according to NCCN Guidelines Version 4.2024-August 22,2024 (T3,N any with clear circumferential resection margin [by MRI]; T1-2,N1-2) [10], (ii) patients undergoing low anterior resection (LAR), (iii) patients who regularly used IN products for 7 days in the preoperative period and patients receiving standard nutrition.Individuals under 18 years of age, pregnant patients, patients with diversion ostomy (diversion ileostomy or diversion colostomy) after surgical resection and anastomosis, patients receiving short-course radiotherapy in the preoperative period, patients with renal failure on dialysis, patients with uncontrolled infection, Patients requiring emergency surgical intervention in the preoperative period, patients with major psychiatric diseases, patients undergoing palliative resection, patients with synchronous tumors other than the primary tumor and metastatic patients, tumors associated with hereditary colo-rectal cancer, and patients who were noncompliant with nutritional therapy were excluded from the study.

Nutrition Formula and Regimen: Immunonutritional enteral formula (Oral Impact RTD, 237mL; Nestle Istanbul, Turkey) contained arginine, omega 3 fatty acids, nucleotides and vitamins. Each 237 ml contains 18 g protein, 9.2 g fat, 44.8 g carbohydrates, 3.3 g dietary fiber, 0.43 g nucleotides, minerals (356 mg sodium, 450 mg potassium, etc.) and vitamins. It was given 3 times a day for 7 days preoperatively, regardless of nutritional status. This feeding regimen is consistent with immune nutrition as prescribed in most clinical trials. Oral intake was started on postoperative day 1 and gradually increased according to tolerance. No patient's oral intake was restricted unless anastomotic leakage and ileus were detected.

Data Collection: Preoperative patient demographic characteristics, comorbidities, previous surgical history, anthropometric data and NRS 2002 (nutrition risk screening) score, postoperative length of stay in the intensive care unit and hospital (number of hospital days after the day of surgery), cost analysis, complications (anastomotic leakage, ileus, superficial or deep surgical site infections, urinary tract infections, respiratory tract infections, venous thromboembolism), reoperation rate, laboratory data (neutrophils, CRP, prealbumin, albumin) and mortality were obtained from electronic health information automation.

Statistical Analysis: IBM SPSS Statistics 22 (IBM SPSS, Turkey) program was used for statistical analyses to evaluate the data collected in the study. The conformity of the parameters to normal distribution was evaluated by Shapiro Wilks test. In addition to descriptive statistical methods (mean, standard deviation, frequency), Student t test was used for comparisons of parameters with normal distribution between two groups and Mann Whitney U test was used for comparisons of parameters without normal distribution between two groups. Repeated measures analysis of variance was used to compare perop -7.day, perop 0.day and postop +7.day levels of normally distributed parameters and Bonferroni test was used to determine the period that caused the difference. Friedman test was used to compare the perop -7.day, perop 0.day and postop +7.day levels of the parameters that did not show normal distribution and Wilcoxon signed rank test was used to determine the period that caused the difference. Fisher's Exact test, Fisher Freeman Halton test and Continuity (Yates) Correction were used to compare qualitative data. Pearson correlation analysis was used to examine

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the relationships between the parameters that conformed to normal distribution. A p value of < 0.05 was considered statistically significant.

3. Results

A total of 66 patients were included in the study and 32 of these patients were regularly receiving immune nutrition products in the preoperative period. The mean age of all patients was 61.2±8.5 years and BMI was 26.11±3.53, with a male/female ratio of 1.35. ASA physical status classification was as follows: I, 16.6% (11); II, 51.51% (34); III, 28.78% (19); IV, 2% (3.03). Demographic data of the patients who received and did not receive IN in the preoperative period are shown in Table 1. Patients who received IN treatment in the preoperative period had significantly higher body mass index than those who did not (p=0.001).

The evaluation of nutritional and biochemical parameters of the patients in the preoperative, preoperative and postoperative periods are shown in Table 2. The evaluation of the differences in the nutritional and biochemical parameters of the patients who received and did not receive IN is shown in Table 3.

Table 1. Patient's Preoperative Demographics and Surgical Characteristics.

Patients Characteristics	**IN Group**	**No IN Group**	**Total**	**p**
	n (%)	**n (%)**	***n (%)***	
Age, mean (SD), year	60,25±8,77	62,09±8,27	61,2±8,5	[1]0,384
Sex				
Male	16 (%50)	22 (%64,7)	38 (%57,6)	[2]0,338
Female	16 (%50)	12 (%35,3)	28 (%42,4)	
BMI, kg/m²,mean (SD)	27,59±3,78	24,76±2,69	26,11±3,53	**[1]0,001***
ASA class				
ASA 1-2	22 (%68,8)	23 (%67,6)	45 (%68,2)	[2]1,000
ASA 3-4	10 (%31,3)	11 (%32,4)	21 (%31,8)	
Comorbidities				
DM	7 (%21,9)	11 (%32,4)	18 (%27,3)	[2]0,497
HT	10 (%31,3)	12 (%35,3)	22 (%33,3)	[2]0,931
CAD	7 (%21,9)	9 (%26,5)	16 (%24,2)	[2]0,882
COPD	6 (%18,8)	6 (%17,6)	12 (%18,2)	[2]1,000
Prior colon or pelvic surgery				
None	19 (%59,4)	19 (%55,9)	38 (%57,6)	[3]0,938
Appendectomy	5 (%15,6)	7 (%20,6)	12 (%18,2)	
Hysterectomy	2 (%6,3)	3 (%8,8)	5 (%7,6)	
Small bowel and colon resections	6 (%18,8)	5 (%14,7)	11 (%16,7)	
Nutrition risk screening 2002 score				

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NRS 2	8 (%25)	10 (%29,4)	18 (%27,3)	[3]0,750
NRS 3	22 (%68,8)	20 (%58,8)	42 (%63,6)	
NRS 4	2 (%6,3)	4 (%11,8)	6 (%9,1)	

[1]Student t test, [2]Yates' continuity correcton, [3]Fisher Freeman Halton test, *p<0.05. HT: Hypertension, DM: Diabetes Mellitus, CAD: Coronary Artery Disease, COPD: Chronic Obstructive Pulmonary Disease, BMI: Body mass index, ASA: American Society of Anesthesiologists Classification.

Table 2. Evaluation of nutritional and biochemical parameters between groups.

Parameters		**IN Group**	**No IN Group**	**Total**	**p[1]**
		mean±SEM	mean±SEM	mean±SEM	
CRP	**Day -7**	1,1±1,05	0,6±0,69	0,84±0,91	[1a]0,053
	Day 0	1,53±1,26	1,98±1,8	1,76±1,56	[1a] 0,447
	Day +7	5,54±3,67	8,29±4,14	6,95±4,13	**[1a] 0,003***
	p[2]	**0,000***	**0,000***		
	(Day-7)-(Day 0) p[2a]	**0,000***	**0,000***		
	(Day -7)-(Day +7) p[2a]	**0,000***	**0,000***		
	(Day 0)-(Day +7) p[2a]	**0,000***	**0,000***		
Neutrophils	**Day -7**	3887,19±1430,11	4353,53±1451,84	*4127,42±1449,38*	[1b]0,194
	Day 0	5291,13±1484,31	4372,94±1377,63	*4818,12±1492,68*	**[1b] 0,011***
	Day +7	5441,88±1212,86	5703,53±1962,29	*5576,67±1635,19*	[1b] 0,515
	p[3]	**0,000***	**0,000***		
	(Day -7)-(Day 0) p[3a]	**0,000***	1,000		
	(Day -7)-(Day +7) p[3a]	**0,000***	**0,001***		
	(Day 0)-(Day +7) p[3a]	1,000	**0,000***		
Prealbumin	**Day -7**	23,13±4,01	24,44±4,05	23,8±4,05	[1b] 0,190
	Day 0	25,44±4,01	22,79±4,37	24,08±4,37	**[1b] 0,013***
	Day +7	14,06±2,94	13,85±4,44	13,95±3,76	[1b] 0,823
	p[3]	**0,000***	**0,000***		
	(Day -7)-(Day 0) p[3a]	**0,000***	**0,000***		
	(Day -7)-(Day +7) p[3a]	**0,000***	**0,000***		
	(Day 0)-(Day +7) p[3a]	**0,000***	**0,000***		
Albumin	**Day -7**	4,1±0,3	4,04±0,32	4,07±0,31	[1b] 0,465
	Day 0	4,23±0,25	4,08±0,27	4,15±0,27	**[1b] 0,017***
	Day +7	3,45±0,61	2,89±0,41	3,16±0,58	[1b] 0,081
	p[3]	**0,000***	**0,000***		

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(Day -7)-(Day 0) p[3a]	**0,001***	0,169
(Day -7)-(Day +7) p[3a]	**0,000***	**0,000***
(Day 0)-(Day +7) p[3a]	**0,000***	**0,000***

Data are expressed as mean ± SEM. CRP; C-reaktive protein. [1a]Mann-Whitney U test, [1b]Student t test, [2]Friedman test, [2a]Wilcoxon signed rank test, [3]Analysis of variance in recurrent measurements, [3a]Bonferroni test, *p<0.05.

Table 3. Evaluation of differences in nutritional and biochemical parameters between groups.

Parameters		**IN Group**	**No IN Group**	**Total**	**p**
		mean±SEM	mean±SEM	mean±SEM	
CRP (median)	**Day 0-Day (-7)** difference	0,44±0,71 (0,3)	1,38±1,63 (0,6)	0,92±1,35 (0,4)	[1]**0,000***
	Day (+7)-Day (-7) difference	4,44±3,4 (3)	7,69±3,67 (7,4)	6,12±3,87 (5,7)	[1]**0,030***
	Day (+7)-Day 0 difference	4±3,35 (2,7)	6,31±4,26 (6,6)	5,19±3,99 (4,4)	[1]**0,000***
Neutrophils	**Day 0-Day (-7)** difference	1403,94±1146,08	19,41±287,25	690,7±1074,47	[2]**0,000***
	Day (+7)-Day (-7) difference	1554,69±1051,01	1350±1972	1449,24±1584,85	[2]0,598
	Day (+7)-Day 0 difference	150,75±1106,62	1330,59±1825,93	758,55±1621,65	[2]**0,002***
Prealbumin	**Day 0-Day (-7)** difference	2,31±1,97	-1,65±1,61	0,27±2,67	[2]**0,000***
	Day (+7)-Day (-7) difference	-9,06±3,06	-10,59±3,39	-9,85±3,3	[2]0,060
	Day (+7)-Day 0 difference	-11,38±3,28	-8,94±3,77	-10,12±3,72	[2]**0,007***
Albumin	**Day 0-Day (-7)** difference	0,13±0,19	0,04±0,1	0,08±0,16	[2]**0,011***
	Day (+7)-Day (-7) difference	-0,65±0,72	-1,16±0,56	-0,91±0,69	[2]**0,002***
	Day (+7)-Day 0 difference	-0,78±0,65	-1,19±0,53	-1±0,62	[2]**0,006***

[1]Mann-Whitney U test, [2]Student t test, *p<0.05.

Table 4 summarizes the complications encountered, length of intensive care and hospital stay and total hospital cost. 4 patients (6.1%) underwent reoperation. Reasons for surgical intervention included anastomotic leakage (n=3) and ileus (n=1). Diverting ostomy was performed in 3 patients with anastomotic leakage. The 4th patient with anastomotic leakage was followed up as a controlled fistula and fistula closed during follow-up. Radiologic percutaneous drainage was performed in 2 patients with intra-abdominal abscess. There was no mortality in the first 30 days postoperatively, in the hospital or after discharge. 7.5% of the patients (5 patients, 2 patients in IN group and 3 patients in No IN group) readmitted after discharge and none of them underwent surgical intervention. The reasons for admission were fever (n=1), diarrhea (n=2), nausea-vomiting (n=1) and ileus (n=1) and there was no significant difference between the two groups.

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Table 4. Postoperative outcomes.

		IN Group	No IN Group	Total	p
		n (%)	n (%)	*n (%)*	
Complications					
	Pulmonary complications	4 (%12,5)	6 (%17,6)	10 (%15,2)	[1]0,734
	Urinary tract infection	6 (%18,8)	7 (%20,6)	13 (%19,7)	[2]1,000
	Wound site infection	5 (%15,6)	11 (%32,4)	16 (%24,2)	[2]0,194
	Intra-abdominal abscess	0 (%0)	2 (%5,9)	2 (%3)	[1]0,493
	Venous thromboembolism	1 (%3,1)	2 (%5,9)	3 (%4,5)	[1]1,000
	Ileus (mechanical or paralytic)	3 (%9,4)	4 (%11,8)	7 (%10,6)	[1]1,000
	Anastomotic leakage	1 (%3,1)	3 (%8,8)	4 (%6,1)	[1]0,614
Hospital mortality					
	Mortality	0 (%0)	0 (%0)	0 (%0)	_
Reoperation					
	Yes	1 (%3,1)	3 (%8,8)	4 (%6,1)	[1]0,614
	No	31 (%96,9)	31 (%91,2)	62 (%93,9)	
Length of stay in intensive care unit (days)		1,33±0,58 (1)	2,5±0,71 (2,5)	1,8±0,84 (2)	[3]0,128
Length of hospital stay (days)		7,53±2,51 (7)	10,82±7,3 (8,5)	9,23±5,73 (8)	[3]**0,022***
Total cost (dollars)		1461,13±500,42	1764,65±465,3	1617,48±502,71	[4]**0,013***

[1]Fisher's exact test, [2]Yates's correction for continuity, [3]Mann whitney U test, [4]Student t test *p<0.05, Data are expressed as mean ± SEM.

There was no statistically significant relationship between total cost and age, ASA score and length of hospitalization (p>0.05, Table 5).

Table 5. Evaluation of the association between total cost and age, ASA and length of hospitalization.

		Total cost (dollars)
Age	**r**	0,194
	p	0,119
ASA	**r**	0,180
	p	0,149
Length of hospital stay	**r**	0,062
	p	0,619

Pearson correlation analysis.

4. Discussion

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Factors such as the patient's general health status, tumour stage, tumour location and pathological subtype are all key considerations in the treatment plan for rectal cancer. For locally advanced rectal cancers, neoadjuvant chemoradiotherapy (Na-CRT) followed by surgery is the universally accepted first-line treatment [11]. Patients undergoing rectal cancer surgery often have slow postoperative recovery, malnutrition, impaired immune function [12]. The use of immunonutrition over the last 2 decades has been controversial, especially its effect on surgical outcomes in patients undergoing major surgery. While one study suggested a reduction in postoperative complications, another study reported no difference between immune nutrition and conventional nutrition [13,14]. In clinical practice, enteral nutrition support prior to or following surgery is the preferred option for patients suffering from malnutrition [15]. However, there is a significant lack of data in the literature on the effects of specific immune nutrition products in the preoperative period, independent of malnutrition, on operative outcomes in patients undergoing surgery for isolated rectal cancer. This study evaluated the effects of preoperative immunonutrition in the early postoperative period in patients who received neoadjuvant treatment then underwent curative surgery without diversion ostomy.

Infections and anastomotic leakage are major postoperative complications for rectal cancer and can lead to poor oncologic outcomes. High nutritional screening score for rectal cancers has been reported to be associated with postoperative anostomotic leakage [16]. In two studies conducted to evaluate the benefits of immunonutrition on colorectal cancer patients within the ERAS protocol, wound infections were found to be reduced and this reduction was significant only in the laparoscopic group [17,18]. In the present study, the majority of cases were open surgeries, and immunonutrition was found to have no effect on infections or anastomotic leakage between the groups. While immunonutrition demonstrated favourable outcomes on certain biochemical markers, its clinical impact was found to be restricted.

The present study found that the duration of hospitalisation and total cost were statistically lower in the immunonutrition group than in the non-immunonutrition group. This phenomenon can be explained as follows: infectious complications, ileus, venous thromboembolism and anastomotic leakage were proportionally lower in the immunonutrition group, although these differences were not statistically significant between the groups.

Our study has several limitations. Firstly, the sample size was low because patients with diversion ostomy were excluded to obtain a homogeneous group, and part of the study was performed during the COVID-19 pandemic. Secondly, most of the cases were open surgeries, so a comparison with laparoscopic surgery was not possible. The study's strength is its well-designed nature and the absence of any conflict of interest between the authors and the industry.

5. Conclusions

Preoperative immunonutrition has been demonstrated to reduce the length of hospital stay and hospital cost in patients with rectal cancer undergoing surgery. However, no benefit has been found with regard to infectious and postoperative complication rates. Further non-industry funded studies are required in order to achieve a more complete understanding of the effect of immunonutrition on rectal surgery in clinical practice.

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Institutional Review Board Statement: Approval for this study was obtained from the local ethics committee of the hospital (HNH, TUEK, Number: 771/03/2019). Between January 2020 and December 2023, 66 patients who

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met the patient selection criteria were included in the study. The study was conducted in accordance with the Declaration of Helsinki.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: We cannot share data due to ethical restrictions.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ESPEN	The European Society for Clinical Nutrition and Metabolism
Globocan	Global Cancer Observatory
IN	Immunonutrition
NCCN	National Comprehensive Cancer Network
NRS	Nutritional Risk Score

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