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The effect of enteral immunonutrition in upper gastrointestinal surgery for cancer: a prospective study

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Background/aim: Enteral feeding and immunonutrition (ImN) have been shown to be associated with a number of favorable effects in patients undergoing cancer surgery. In this prospective study, we aimed to assess the perioperative use of enteral immunonutrition in patients undergoing radical gastrointestinal surgery for malignancy.

Materials and methods: Forty-one patients with malignancy were included in this study and were randomized into one of the two following nutritional strategies: enteral only (EN) or enteral with enteral immunonutrition (ENIN). These regimens were followed for 7 days perioperatively by all patients. Nutritional parameters and postoperative morbidity, mortality, and length of hospital stay (LHS) were assessed.

Results: Serum prealbumin levels increased significantly in the ENIN group (P = 0.033). Moreover, patients in the ENIN group showed a more marked decrease in the rate of postoperative infections (P = 0.021) and anastomotic leakage (P = 0.018) than patients fed with EN. In the EN group, LHS was significantly longer than that in the ENIN group (18 vs. 12 days) (P = 0.032). Rates of overall morbidity and mortality were similar in the two groups (P > 0.05).

Conclusion: ENIN was found to have a favorable effect on the outcome of radical gastrointestinal surgery for malignancy. Meticulous preoperative assessment of malnutrition and at least a 7-day perioperative enteral use can increase the effectiveness of immunonutrition.

Key words: Immunonutrition, enteral, gastrointestinal surgery, cancer

1. Introduction

Energy and protein depletion with consequent malnutrition is a common occurrence in patients with gastrointestinal cancers (1,2) and represents a major cause of morbidity, mortality, and decreased survival (3).

During the course of malignancies, more than 50% of the patients experience significant weight loss. Depletion of body stores in conjunction with dysfunctional protein synthesis and immune response result in the impairment of wound healing and body resistance against infections (4,5), increasing the risk of postoperative complications and prolonged hospital stay in this group of patients (6). Replacement of the body stores after an initial assessment of malnutrition status and cachexia caused by cancer has recently become a more popular perioperative nutritional strategy (7). Nutritional therapy is carried out either by parenteral nutrition (Pn) or enteral feeding (Ef), and the latter is generally more frequently preferred by surgeons owing to certain advantages over Pn, including being safer and having more physiological and economic benefits (8,9).

Immunonutrition (ImN) consists of arginine supplementation combined with glutamine, a leucine metabolite hydroxy-methyl-butyrate (HMB), omega-3 fatty acids, and ribonucleic acid. These immunonutrients, in addition to protein turnover modulation, enhance wound healing and immune functions (10–12), resulting in decreased rates of surgical site infections, other infectious complications, and shortened hospital stay after gastrointestinal cancer surgery (13,14). Previous studies on ImN have examined several of its aspects such as the timing (pre-/postoperative or both), the route of replacement (parenteral/enteral), benefits, and the decisive threshold of malnutrition following which such nutritional strategies are beneficial (15–17).

Previous studies have already looked at the role of ImN in different types of gastrointestinal malignancies. The aim of this prospective study was to evaluate the effects

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of perioperative use of enteral ImN (ENIN) in upper gastrointestinal cancer surgery involving malignancies above the Treitz's ligament.

2. Materials and methods

This prospective, randomized study was undertaken at the Department of Surgery, Derince Training and Research Hospital, Kocaeli, Turkey, between January 2012 and February 2013. Forty-one patients with malignancies of the upper gastrointestinal tract were included. The study protocol was approved by the local ethics committee and informed consent was obtained from all patients. The purpose of the study was to evaluate the effect of perioperative ENIN on morbidity (overall and specific incidence of complications), mortality, and length of hospital stay (LHS) after elective radical gastrointestinal surgery. The following two nutritional strategy groups were defined: enteral only (EN) and ENIN. While both groups of patients were provided with enteral nutrition perioperatively, patients in the ENIN group also received additional ImN. Following nutritional status assessment, patients were randomly assigned into one of the two nutrition groups. The nutritional team that organized the two nutrition regimes was blind to the groups.

2.1. Patients, inclusion criteria

Malignancies for study inclusion included cancers of the distal esophagus, stomach, and head of the pancreas. Exclusion criteria included stage 4 malignancies; coexistent severe lung, kidney, heart, or liver diseases; age less than 18 or greater than 75 years; and nutritional therapy intolerance. Nutritional status and malnutrition severity were evaluated using patient history, subjective global assessment (SGA), and laboratory tests. The body mass index (BMI) was also estimated preoperatively. Nutritional support was carried out in patients with unintentional weight loss exceeding 10% of their bodyweight and in those with a SGA group of B or C. Laboratory tests to evaluate the nutritional status in each patient included plasma albumin, prealbumin, and transferrin. In addition, the complete blood count (CBC) and biochemical markers of organ functions (plasma urea, creatinine, aspartate and alanine amino transferase, bilirubin, sodium, potassium, calcium, etc.) were analyzed.

2.2. Surgical interventions

Several procedures such as distal esophagectomy, total or subtotal gastrectomy, or pancreaticoduodenectomy were implemented according to the malignancy. In patients with gastric cancer, standard D2 lymph node dissection was also performed. For antibiotic prophylaxis cefazolin sodium 1 g i.v. was given 30 min prior to surgery. Repeated doses were administered if surgery time exceeded 4 h.

2.3. Nutritional support and assessment

Nutritional support was provided for 7 days before and 7 days after the intervention. Although oral route was the initial choice of nutrition preoperatively, tube feeding was also used in patients with insufficient oral intake. While enteral nutrition was accomplished with Ensure Plus (Abbott Nutrition) in both groups, Abound (Abbott Nutrition) was used in the ENIN patients for ImN. The list of ingredients found in these nutritional products is given in Table 1. Immunonutrient protocol, i.e. Abound, was administered 2 times a day in 250 mL of watery solution. Adequate amounts of two main immunonutrients, glutamine (>14 g/day) and arginine (>12 g/day), were provided in the ENIN group.

Patients' energy requirements were calculated using the Harris–Benedict formula. Postoperative energy replacement did not exceed 30 kcal/kg per day. Postoperative protein requirement was set at 2 g per kg of body weight. Following surgery, nutritional protocols were initiated after 24 h using nasoenteral or feeding jejunostomy tubes. Postoperatively, EN was given at a dose of 30 mL/h on day 1, followed by 50 mL/h on day 2, and the target dose was reached on postoperative day 3. All patients received EN or ENIN for a minimum duration of 7 days postoperatively. Nutritional support was continued in patients who had ineffective/inadequate oral intake at hospital discharge. On preoperative day 1, postoperative day 6, and postoperative day 8 total blood counts and biochemical assays were performed.

2.4. Investigational parameters

The purpose of the present study was to investigate the effects of perioperative use of ImN on postoperative morbidity, mortality, and LHS. Mortality was defined as death occurring within 30 days after hospitalization. LHS was defined as the duration of time from the day of surgery until the day of discharge. Other variables such as duration

Table 1. Ingredients of the feeding solutions.

Nutrients	Abound*	Ensure Plus**
Proteins (g)	14.8	15.6
L-arginine	7.4	-
L-glutamine	7.4	-
HMB	1.3	-
Carbohydrates (g)	7.8	50.5
Lipids (g)	0.02	12.3
Energy (kcal)	91	375

*each 24-g sachet.
**per 250 mL.

of operation, requirement for blood transfusions, and nutritional parameters were recorded.

2.5. Statistical analysis

All data were collected and analyzed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). Within-group differences were analyzed using the paired t test and differences between groups were analyzed using the Mann–Whitney U test and chi-square test, where applicable. $P < 0.05$ was considered significant.

3. Results

In a 13-month period, 41 patients (22 male, 19 female) were included in the study. Various baseline parameters (such as the demographic characteristics of the patients) are shown in Table 2. There were no significant differences between the two groups in terms of age, sex, nutritional parameters, or surgical characteristics.

Nutritional status was evaluated by perioperative assessment of plasma albumin, prealbumin, and transferrin (Table 3). Although an increasing trend was observed in all of these parameters in both groups, only the change in prealbumin in group ENIN reached statistical significance ($P = 0.033$). The percent increase in transferrin levels was higher as compared with plasma albumin in patients with ImN, although the difference was not significant ($P = 0.125$). EN did not appear to have a favorable impact on these variables. Infectious complications occurred at a significantly lower frequency in the ENIN patients than in the EN patients (11.7% vs. 31.3%, $P = 0.021$). In addition, a positive effect of ImN on LHS was observed, with significantly shorter postoperative LHS in the ENIN group than in the EN group (12 vs. 18 days, $P = 0.032$). In our study, morbidity and mortality rates, which represent important outcomes after surgery, did not differ significantly between the EN and ENIN groups ($P > 0.05$) (Table 4).

A subgroup analysis of postoperative complications found significantly lower rates of surgical site, pulmonary, and urinary infections among ENIN patients ($P < 0.05$) (Table 5). The two groups were similar in terms of the occurrence of other morbid conditions ($P = 0.642$).

A major surgical complication was anastomotic leakage, which occurred at a significantly lower rate in the ENIN group than in the EN group ($P = 0.018$).

Table 2. Comparison of baseline demographic, nutritional, and surgical characteristics.

	EN	ENIN	P
N	20	21	0.809
Age	62.6 ± 9.1	64.05 ± 9.04	0.645
Sex (M/F)	14/6	15/6	0.703
BMI (kg/m^2)	21.1 ± 2.1	22 ± 1.98	0.572
Origin of malignancy			
Distal esophagus	6	4	0.455
Gastric	11	13	0.542
Pancreatic head	3	4	0.485
Surgical operations			
Distal esophagectomy	5	4	0.655
Total gastrectomy	11	13	0.437
Subtotal gastrectomy	6	4	0.399
Pancreaticoduodenectomy	3	4	0.485
Operative time (min)	205 ± 11.2	210 ± 10.7	0.424
Blood transfusions (patients/group)	15	16	0.782
Albumin (g/dL)	3.1 ± 0.52	3.2 ± 0.3	0.651
Prealbumin (mg/dL)	21.3 ± 1.1	22.1 ± 0.95	0.309
Transferrin (mg/dL)	205 ± 4.5	208 ± 38	0.286

Table 3. Change in nutritional parameters of the study period.

	Preop. day 1	Preop. day 7	Postop. day 7	P
EN				
Albumin	2.96 ± 0.3	2.99 ± 0.32	3 ± 0.33	0.433
Prealbumin	19.2 ± 0.4	20.1 ± 0.22	21.1 ± 0.20	0.254
Transferrin	192.5 ± 10.2	194.2 ± 11.1	195.5 ± 12.1	0.386
ENIN				
Albumin	2.95 ± 0.4	3.02 ± 0.25	3.05 ± 0.28	0.644
Prealbumin	20 ± 2.4	29.6 ± 2.03	28.1 ± 1.63	0.033
Transferrin	201 ± 15.1	214 ± 10.1	211 ± 8.9	0.125

Table 4. Rates of infectious complications, morbidity, mortality, and LHS.

	EN	ENIN	P
Infectious complications	16 (31.3%)	6 (11.7%)	0.021
Overall morbidity	31 (60.8%)	20 (39.2%)	0.442
Mortality	2 (4.8%)	1 (2.4%)	0.216
LHS (days) (median)	18 (9–54)	12 (8–49)	0.032

Table 5. Detailed list of postoperative complications.

	EN	**ENIN**	**P**
Infectious complications	16 (31.3%)	6 (11.7%)	0.021
Surgical site infection	5	2	0.013
Pulmonary infection	4	1	0.008
Urinary tract infection	3	1	0.020
Abdominal abscess	1	0	0.315
Sepsis	1	1	1
Venous catheter infection	2	1	0.253
Noninfectious complications	15 (29.5%)	14 (27.5%)	0.642
Anastomotic leakage	3	1	0.018
Wound dehiscence	2	2	1
Renal failure	2	2	1
Respiratory failure	3	2	0.614
Bleeding	0	1	0.315
Pancreatic fistula	2	1	0.252
Delayed gastric emptying	2	3	0.614
Circulatory failure	2	2	1

4. Discussion

Nutrition is a fundamental component of human health. In individuals with malnutrition or specific nutritional deficiencies such as protein-energy malnutrition, postsurgical recovery is generally more problematic and poses significant health risks. Surgical procedures represent a trauma for the organism, even in healthy subjects, and cancer patients undergoing surgical interventions are generally more vulnerable to life-threatening complications, with predictably more disappointing results.

Cancer patients frequently suffer from a number of nutrition-related conditions such as malnutrition, cancer cachexia, immune dysfunction, and inadequate wound healing, which may have major effects on postoperative morbidity and mortality (18,19). Thus, it is not surprising to see that the role of nutritional support in patients undergoing surgery has been extensively studied in the last two decades. In this regard, Ef offers significant advantages over Pn in this group of patients. As compared to Pn, enteral formulations are less costly and have more physiological impact. For instance, the maintenance of gastrointestinal tract functionality in patients receiving enteral nutrition helps prevent gut mucosal atrophy and bacterial translocation (20–22), potentially diminishing septic complications (23), which are among the most dreaded postoperative complications. Recently, the preferred route of administration of Ef involves the use of nasoenteral tubes or feeding jejunostomy tubes. Pn is generally reserved for patients who require complete bowel rest due to conditions such as intestinal obstruction, stercoral fistula, or an active episode of inflammatory bowel disease (24). Its advantages include practical and quick administration, rapid replacement of protein-energy demand, and moderate to high patient compliance.

On the other hand, the established advantages of Ef render it the nutritional route of choice in the perioperative period. Accordingly, the American Society for Parenteral and Enteral Nutrition (ASPEN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), the two leading societies in the field of nutrition, endorse the use of enteral nutrition, particularly during the perioperative period (25,26).

Favorable effects of ImN, particularly in cancer patients, partly arise from its effects on host defense and protein synthesis, which ultimately result in the modulation and increased levels of immune parameters such as complements, immunoglobulins, interleukins, lymphocytes, and natural killer cells (27–30).

These effects are associated with a reduction in the rate of infections and LHS in patients undergoing radical gastrointestinal surgery (13,14). In addition, the use of ImN in elective gastrointestinal cancer surgery reduces hospital costs through decreased rates of postoperative complications and LHS (31). The beneficial effects of nutritional support are more prominent when enteral nutrition is used perioperatively.

Despite these beneficial effects, the effects of ImN on mortality and overall complication rates have not been demonstrated (15,32,33). Although ImN has beneficial effects in major cancer surgery, it may also be associated with certain detrimental effects, particularly in critically ill patients (34–36).

The benefits of Ef and ImN in terms of hospital costs, postoperative infectious complications, and patient physiology have prompted us to use them in combination and design this particular study.

In different studies performed, the duration of nutritional support ranged between 3 and 14 days (37–39). Some studies propose a minimum duration of 5 days for ENIN preoperatively in gastrointestinal surgery patients to observe a beneficial effect (33,40,41). Based on these suggestions, perioperative nutritional support in the form of ImN was administered for 7 days in our patients.

Abound is an immunonutritional product that contains glutamine, arginine, and HMB. The beneficial effects of these specific nutrients were previously described in cancer cachexia and malnutrition, collagen synthesis, wound healing in renal failure, hematological parameters in malignancy, and in AIDS patients (42–45). The same feeding combination has never been used in upper gastrointestinal cancer surgery previously.

Patient selection is also an important consideration in determining the appropriate nutritional support strategy. In cancer patients, preoperative nutritional support is generally required in the case of malnutrition and malignant cachexia. It appears that some of the previous studies did not fully take the issue of nutritional status into consideration. Due to the absence of obvious favorable effects of ImN in well-nourished patients (15,16,32), the nutritional status of patients was initially evaluated and nutritional support was only given to patients with cancer-related moderate or severe malnutrition in our study.

In the present study, favorable effects of ENIN were found on the postoperative infectious complication rate and nutritional parameters. Surgical site, pulmonary, and urinary tract infections occurred at a significantly lower rate in patients fed with ENIN ($P < 0.05$), consistent with previous reports (12,46,47).

Anastomotic leakage represents a serious postoperative complication in gastrointestinal surgery and there was a significantly lower incidence of anastomotic dehiscence in our ENIM patients, similar to a recent report (48).

The nutritional status of the patients was assessed using plasma albumin, prealbumin, and transferrin levels. In both study groups, there was an increasing trend in

all these laboratory parameters. However, only plasma prealbumin levels showed a significant increase in the ENIN group (P = 0.033). Previous similar studies reported an improvement in certain nutritional parameters such as serum prealbumin and/or transferrin levels (8,9).

LHS, morbidity, and mortality rates are other important indicators in the efficiency assessment of ImN. In this regard, despite a significant effect of ImN on LHS, no change in mortality or overall complications could be demonstrated in patients undergoing gastrointestinal surgery (13,15,33). In our study, ENIN was associated with a significant reduction in LHS (P = 0.032). This may be due to the decrease in the rates of postoperative infection and anastomotic leakage. On the other hand, neither nutritional regimen had an effect on the overall morbidity and mortality rates (P > 0.05)

In conclusion, a number of different beneficial effects of ImN were observed in patients undergoing radical upper gastrointestinal surgery in this prospective study. The rate of postoperative infectious complications, LHS, and serious morbidity such as anastomotic dehiscence were significantly lower in patients fed ENIN perioperatively than in those fed EN. Factors that determine the success of this particular nutritional regimen include the timing and duration of nutrition, the route of replacement, and the severity of malnutrition. In this regard, a meticulous preoperative assessment of nutritional status in cancer patients is essential. In well-nourished cancer patients and for short-term supplementation, this strategy may be futile. However, preoperative enteral nutrition with ImN for a minimum duration of 7 days may offer certain advantages in terms of the outcome of cancer surgery when the patient is malnourished.

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