Ann Surg Oncol (2013) 20:3912–3918
DOI 10.1245/s10434-013-3088-1

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Clinical and Immunological Impact of Early Postoperative Enteral Immunonutrition After Total Gastrectomy in Gastric Cancer Patients: A Prospective Randomized Study

Luigi Marano, MD, Raffaele Porfidia, MD, Modestino Pezzella, MD, Michele Grassia, MD, Marianna Petrillo, MD, Giuseppe Esposito, MD, Bartolomeo Braccio, MD, PierLuigi Gallo, MD, Virginia Boccardi, MD, Angelo Cosenza, MD, Giuseppe Izzo, MD, and Natale Di Martino, MD

8th General and Gastrointestinal Surgery—Department of Internal Medicine, Surgical, Neurological Metabolic Disease and Geriatric Medicine, Second University of Naples, Naples, Italy

ABSTRACT

Background. Enteral immunodiet has been gaining increasing attention, but experimental data of its clinical effects in patients with gastric cancer are inconsistent, contradictory, and poorly investigated. The aim of this study was to assess the impact of early postoperative enteral immunonutrition on clinical and immunological outcomes in a homogeneous group of gastric cancer patients submitted to total gastrectomy.

Methods. A total of 109 patients with gastric cancer were randomized to receive early postoperative enteral immunonutrition (formula supplemented with arginine, omega-3 fatty acids and ribonucleic acid [RNA]), or an isocaloric–isonitrogenous control. The postoperative outcome was evaluated based on clinical variables, including postoperative infectious complications, anastomotic leak rate, and length of hospitalization. In addition, state of cellular immunity was evaluated and compared between the 2 groups.

Results. The incidence of postoperative infectious complications in the immunodiet group (7.4 %) was significantly ($p < .05$) lower than that of the control group (20 %), as well as the anastomotic leak rate (3.7 % in immunodiet group vs 7.3 % in standard nutrition group, $p < .05$). Mortality rate did not show any significant differences; patients of the immunodiet group were found to have a significantly reduced length of hospitalization (12.7 ± 2.3 days) when compared with standard diet group (15.9 ± 3.4 days, $p = .029$). The data on cellular immunity showed that the postoperative $CD4^+$ T-cell counts decreased in both groups, but the reduction in the IED group was significantly higher ($p = .032$) compared with the SND group.

Conclusions. Early postoperative enteral immunonutrition significantly improves clinical and immunological outcomes in patients undergoing gastrectomy for gastric cancer.

Malnutrition is usually associated with humoral and cellular immune function depression, inflammatory response alterations, and a delay or failure of the wound-healing process. Thus, patients requiring elective surgery for neoplastic disease of the upper digestive tract often present a high incidence of serious complications, mostly infectious complications, during the early postoperative period and during an extended hospitalization.[1–6]

In particular, outcomes of patients submitted to surgery for gastric cancer, as complications of surgical anastomosis sealing processes and surgical wounds healing stages, are significantly affected by malnutrition throughout the suppression of the immune function and the exaggeration of a stress response and organ dysfunction.[7] Even if surgical resection is the mainstay of curative treatment for gastric cancer, total gastrectomy is associated with postoperative catabolism, and changes in the metabolic, endocrine, neuroendocrine, and immune system that contribute to high postoperative morbidity rates in more than 40 %.[8–10] The American Society of Parenteral and Enteral Nutrition recommended the use of preoperative nutritional therapy in

First Received: 31 January 2013;
Published Online: 10 July 2013

L. Marano, MD
e-mail: marano.luigi@email.it

malnourished patients undergoing major gastrointestinal surgery.[11,12] In particular, enteral nutrition has been considered the treatment of choice, not only in malnourished patients but also in the well-nourished patients, because of its cost efficiency and lower complication rate compared with parenteral nutrition.[13–16] Moreover, an enteral immunonutritional diet, defined as a diet formula enriched with arginine, glutamine, omega-3 fatty acids, and nucleotides (ribonucleic acid [RNA]), has been gaining increasing attention.[8,17–21]

Studies using these immune-enhanced formulas in the early postoperative period have invariably demonstrated significant improvements in the patient's immunological status and inflammatory response.[18,22–27] However, the detailed mechanism of immunonutrition subtending more favorable clinical outcomes are still unclear, although it has been demonstrated that this enriched diet can induce an alteration of cytokine production and immune function, thereby limiting the undesirable perioperative excessive stimulation of the immune and inflammatory cascade.[28]

A recent meta-analysis and a systematic review of the clinical outcome demonstrated that patients treated with immunonutrition present better prognosis and a reduction in the number of infectious complications than those treated with standard enteral nutrition.[18,29]

However, experimental data of immunonutrition in patients with gastric cancer are inconsistent, contradictory, and poorly investigated. Some have reported reduced infective complications and shortened hospital stays, whereas others have found no advantages.[14,22,25,30–37] These studies are confounded by heterogeneous groups of patients with cancer and numerous centers recruiting small numbers of patients.[14,25,32]

To address those ambiguities and to verify the actual clinical significance, the primary aim of the present prospective randomized study was to assess the impact of early postoperative enteral immunonutrition on clinical outcome in a homogeneous group of gastric cancer patients submitted to total gastrectomy. A secondary aim was to study the immunological effects of immunonutrition in these patients, with a particular focus on $CD4^+$ and $CD8^+$ T-cell immunity.

MATERIALS AND METHODS

The study was a 2-arm, randomized controlled clinical trial conducted to assess the impact of enteral immunonutrition on clinical outcomes in patients undergoing gastrectomy for cancer. The work was set at the Eighth General and Gastrointestinal Surgical Centre and was carried out between 2006 and 2011.

Patients with histologically documented gastric adenocarcinoma who were candidates for elective total gastrectomy were enrolled. Exclusion criteria were previous abdominal radiotherapy; preoperative chemotherapy; pulmonary, cardiovascular, renal, or hepatic disease; diabetes; history of recent immunosuppressive therapy or immunological diseases; and ongoing infection, as several authors previously described.[25,31,33] After applying the exclusion criteria, a total of 109 patients were enrolled in this study. Nutritional status was assessed according to ESPEN guidelines.[38] All patients underwent standardized total gastrectomy with spleen-preserving modified radical D2 lymphadenectomy according to Japanese Classification of Gastric Carcinoma.[39] However, splenectomy was necessarily performed in a total of 13 patients (11.9 %) to ensure complete dissection of the splenic hilar lymph nodes in very difficult dissection cases. The reconstruction of the alimentary tract was performed by an end-to-side esophagojejunostomy and an end-to-side Roux-and-Y jejunojejunostomy, with prophylactic ceftriaxone and metronidazole at induction and 2 postoperative doses, treated with early enteral postoperative nutrition delivered via a fine needle catheter jejunostomy placed 30–40 cm to the distal Roux-and-Y jejunojejunostomy.

Two groups of patients were then randomly obtained based on postoperative enteral nutrition. In the first group of 54 patients (immunoenriched diet [IED] group) an enteral immunoenriched nutrition was administered (Impact, Novartis Consumer Health, Berne, Switzerland), while in the second group of 55 patients (standard enteral nutrition [SEN] group) was administered an enteral standard nutrition (Jevity 1 Cal, Abbott Nutrition, Cleveland, OH) without immunonutrients. The nutritional formulations of both groups were isonitrogenic and isoenergetic (1 kcal/1 mL). Nutrition through jejunostomy was introduced in both groups 6 h after the surgery until the seventh postoperative day, beginning with an infusion of 10 mL/h with an increasing rate of 10 mL/h every 12 h, until the maximum feed target rate of 80 mL/h was achieved corresponding to target individual of 35 kcal/kg/day. Both groups received the same postoperative care, and none of the patients received concomitant parenteral nutrition.

After surgery, blood transfusions and derivatives, as well as replacement and/or integration of antibiotic therapy, were performed when clinically required. On the seventh postoperative day a fluoroscopically controlled swallow of water-soluble contrast medium was done to assess the esophagojejunostomy. Thereafter, oral feeding using first liquid and then semiliquid food was begun in both groups. In the case of anastomotic dehiscence, oral intake was kept up according to the individual situation.

Mortality was recorded when it occurred during hospitalization. The postoperative length of stay was defined as the number of days between intervention and discharge.

TABLE 1 Clinical and surgical baseline characteristics of the 2 groups

	Immunoenriched diet ($n = 54$)	p value	Standard enteral nutrition ($n = 55$)
Age mean (years); (range)	66.6 (55–78)	.557	65.1 (49–83)
Male/female (n)[a]	34/20	.523	37/18
Body mass index mean (kg/m^2) ± SD	23.1 ± 2.8	.518	23.6 ± 3.5
Malnourished patients (n)	33 (61)	.479	30 (54)
Operative time mean (minutes) ± SD	310 ± 46	.659	367 ± 43
Operative blood loss mean (mL) ± SD	340 ± 54	.456	364 ± 21
Tumor status			
T1	2 (3.7)	.423	3 (5.4)
T2	19 (35.2)	.546	17 (30.9)
T3	26 (48.2)	.535	28 (50.9)
T4	7 (12.9)	.534	7 (12.7)
Node status			
N0	26 (48.1)	.465	28 (50.9)
N1	17 (31.5)	.352	15 (27.3)
N2	8 (14.8)	.613	8 (14.5)
N3	3 (5.6)	.456	4 (7.3)
Resection type			
R0	52 (96.3)	.659	54 (98.2)
R1–2	2 (3.7)	.612	1 (1.8)

Values in parentheses are percentages unless indicated otherwise

SD standard deviation, *n* number of patients, *mL* milliliters

[a] χ^2 test M versus F: $p = .523$

Postoperative complications, defined according to the criteria established by the American College of Chest Physicians, were recorded during hospitalization [40]:

- Systemic inflammatory response syndrome: 2 or more of the following criteria: (1) temperature >38 or <36 °C, (2) heart rate >90 beats/min, (3) respiration >20/min or $PaCO_2 < 32$ mmHg, (4) leukocyte count >12,000/mm^3, <4,000/mm^3, or >10 % band cells
- Sepsis: SIRS plus infection microbiologically confirmed
- Wound infection: redness or tenderness of surgical wound, with the discharge of pus
- Anastomotic leakage: dehiscence of anastomosis proven with radiology
- Respiratory tract infection: abnormal chest radiograph, with fever (temperature >38 °C) and white blood cell count >12 × 10^3/L and positive sputum or bronchoalveolar lavage
- Urinary infection: clinical symptoms associated with bacteriuria (>100.000 colony forming units)

To determine the nutritional parameters (protein, albumin, and transferrin), blood was obtained from a cubital vein 1 day before surgery (baseline) and on postoperative days (PODs) 1, 3, and 7.

The number of leukocytes, lymphocytes, CD4$^+$ T-cells, and CD8$^+$ T-cells was assessed the day before surgery (PrOD) and 1 and 7 PODs. For the flow cytometric assays, peripheral venous blood samples were collected in EDTA-containing tubes. The number of CD4$^+$ T-cells and CD8$^+$ T-cells was measured using the anti-human CD4 monoclonal antibody and anti-human CD8 monoclonal antibody, respectively. The values measured at each preoperative and postoperative time point were compared to evaluate the effect of surgery on the changes of each variable.

The study was approved by the ethics committee of Second University of Naples and conducted according to the ethical standards of the Helsinki Declaration. Each patient gave informed written consent.

Calculations and Statistical Analysis

The observed data were normally distributed and presented as mean ± SD. In order to investigate the difference in clinical and immunologic parameters between the 2 groups, sample size calculation was estimated on an IBM PC computer by GPOWER software. The resulting total sample size, estimated according to a global effect size of 25 % with type I error of 0.05 and a power of 81 % was 104 patients, 52 patients for each group.

A statistical data analysis was performed using SPSS (SPSS Inc., Chicago, IL). The repeated measure ANOVA, t test, and the Mann–Whitney U test were used to compare continuous variables. The χ^2 test was used to compare discrete variables. Statistical significance was considered to be $p < .05$.

TABLE 2 Postoperative outcomes

	Immunoenriched diet ($n = 54$)	Standard enteral nutrition ($n = 55$)	p value
SIRS (days)	1.1 ± 0.89	2.2 ± 1.02	.036
Patients with infectious complications	4 (7.4 %)	11 (20 %)	.041
Wound infection	1 (1.8 %)	3 (5.4 %)	
Respiratory tract infection	2 (3.7 %)	5 (9 %)	
Urinary tract infection	1 (1.8 %)	2 (3.6 %)	
Sepsis	0	1 (1.8 %)	
Mortality	1 (1.8 %)	1 (1.8 %)	.325
Anastomotic leakage	2 (3.7 %)	4 (7.3 %)	.045
Length of hospitalization (days)	12.7 ± 2.3	15.9 ± 3.4	.029

SIRS systemic inflammatory response syndrome

TABLE 3 Comparison of early and late postoperative period complications between IED and SEN groups

	Immunoenriched diet ($n = 54$)	Standard enteral nutrition ($n = 55$)	p value
Infectious complications	4 (7.4 %)	11 (20 %)	
Early postoperative period	3 (5.5 %)	3 (5.4 %)	.684
Late postoperative period	1 (1.8 %)	8 (14.5 %)	.021

χ^2 test

RESULTS

A total of 109 patients were enrolled into the study. Stratifying subjects according to postoperative enteral nutrition in immunoenriched diet (IED) group and standard enteral nutrition (SEN) group showed no significant differences in the baseline characteristics between the 2 groups (Table 1). Tolerance of the postoperative diet formulas was excellent in both groups, and there were no discontinuations due to intolerance. During the postoperative period, some patients reported diarrhea and abdominal bloating, but the nutritional goal was reached in all patients.

As shown in Table 2, the duration of SIRS in the IED group (1.1 ± 0.89 days) was significantly shorter than that in the SEN group (2.2 ± 1.02 days, $p = .036$). The incidence of infectious complications and the anastomotic leak rate were found to be statistically significantly reduced in the immunoenriched diet group. Additionally, comparison of infectious complications occurred in "early postoperative period" (including 5 days after surgery) and "late postoperative period" (from sixth postoperative day until to discharge) did not show any differences between "early" groups ($p = .684$).

In the "late postoperative period" a lower complication rate was registered in immunoenriched diet group compared with standard enteral nutrition diet group (1.8 vs 14.5 %, $p = .021$) (Table 3).

Mortality rate did not show any significant differences (1.8 % in each group, due to postoperative heart attack); patients of the IED group were found to have a significantly reduced length of hospitalization (12.7 ± 2.3 days) compared with the SEN group (15.9 ± 3.4 days, $p = .029$).

Baseline nutritional variables (protein, albumin, and transferrin) were comparable among the 2 groups (Table 4), even noting significant decreases of the 3 parameters compared with the baseline, with tendency to normalization at postoperative day 7.

The data on cellular immunity showed that the postoperative $CD4^+$ T-cell counts decreased in both groups, but the reduction in the IED group was significantly higher ($p = .032$) compared with the SND group. No other significant difference was observed on PrOD and postoperative day 7 between the 2 groups. Total leukocyte, lymphocyte, and $CD8^+$ T-cell did not show any significant differences (Table 5).

DISCUSSION

Malnutrition and major surgery in gastric cancer patients are well-known factors capable of impairing the immunological functions, contributing to an increased risk of postoperative infectious, anastomotic trouble, and metastasis after surgery.[41–43] During the last 15 years the role of the gastrointestinal tract in host defense has been emphasized, and early enteral feeding has been favored over parenteral feeding after abdominal surgery.[44,45] The primary goal of nutritional care has changed from the provision of necessary calories to cover a patient's needs to approaches aimed at restoring optimal metabolic and immune responses.[8] Furthermore, immunomodulatory formulas supplemented with arginine, glutamine, omega-3 fatty acids, and nucleotides have gained increasing attention because of their ability to reduce the rate of postoperative complications compared with standard nutritional formulas.[18–21] There have also occurred, however, criticism concerning immunonutrition. In 1992, Daly et al.[23,46] found a significant decrease in the infectious complication rates in the patients undergoing major operation for the upper gastrointestinal malignancies

TABLE 4 Nutritional variables

	Immunoenriched diet ($n = 54$)	Standard enteral nutrition ($n = 55$)
Protein g/L		
Baseline	6.5 ± 1.2	6.8 ± 0.9
POD1	4.3 ± 1.6[a]	4.1 ± 1.3[a]
POD3	4.6 ± 1.8[a]	4.2 ± 1.6[a]
POD7	5.6 ± 1.4	5.4 ± 1.9
Albumin g/L		
Baseline	3.4 ± 1.6	3.2 ± 0.8
POD1	2.6 ± 1.1[a]	2.5 ± 1.2[a]
POD3	2.9 ± 1.6	2.7 ± 1.5
POD7	3.1 ± 1.4	3.0 ± 1.2
Transferrin mg/dL		
Baseline	320.2 ± 12.1	341.5 ± 9.2
POD1	210.9 ± 10.5[a]	214.4 ± 9.4[a]
POD3	214.3 ± 9.6[a]	221.7 ± 8.4[a]
POD7	236.7 ± 8.4	234.8 ± 9.1

Repeated measure ANOVA. Data are expressed as mean ± standard deviation

POD postoperative day

[a] $p < .05$ versus baseline

TABLE 5 Cellular immunity assessment

	Immunoenriched diet ($n = 54$)	Standard enteral nutrition ($n = 55$)	p value
Leukocytes (/μL)			NS
PrOD	6.800 ± 356	7021 ± 298	
POD1	12103 ± 387	13265 ± 241	
POD7	7103 ± 256	8032 ± 301	
Lymphocytes (/μL)			NS
PrOD	2356 ± 154	3025 ± 243	
POD1	3985 ± 231	4441 ± 312	
POD7	1562 ± 203	2994 ± 260	
$CD4^+$ T-cell (/μL)			.032
PrOD	523 ± 64	601 ± 89	
POD1	985 ± 32	1023 ± 46	
POD7	352 ± 45	542 ± 53	
$CD8^+$ T-cell (/μL)			NS
PrOD	356 ± 41	544 ± 65	
POD1	578 ± 56	745 ± 54	
POD7	294 ± 37	488 ± 71	

Repeated measure ANOVA (mean ± standard deviation)

PrOD preoperative day, *POD* postoperative day, *NS* not significant

treated with postoperative immunonutrition. In 1997, Heslin et al.[37] compared early postoperative immunonutrition with no nutritional support in the patients with upper gastrointestinal malignancies. In this study, postoperative immunonutrition was not beneficial. In 2002, Gianotti et al. and Braga et al.[31,33] observed that perioperative immunodiet resulted in the best outcome in 150 malnourished (weight loss >10 % over 6 months) surgical gastrointestinal cancer patients, while in 305 well-nourished patients, preoperative administration of immunonutrition was as effective as the perioperative immunonutrition. Meta-analysis by Heys (11 trials, 1009 patients) and Beale (12 trials, 1482 patients) in 1999, Heyland (22 trials, 2419 patients) in 2001, and Sacks (7 trials, 1058 patients) in 2003 showed that immunonutrition was associated with significantly fewer infectious complications and a shorter length of hospital stay in elective surgical patients without impact on mortality.[18,19,29,46,47] There may be numerous reasons that could explain these discrepancies. Firstly, many studies, in which immunomodulating nutritional intervention showed no clinical effect were performed on well-nourished patients, while works demonstrating reduction of complications included moderately or severely malnourished patients.[8,48,49] Secondly, the heterogeneity of study groups in various clinical studies concerning immunonutrition is clear.[8,19,23,25,31–33,48,50]

A strength of the present study, compared with previous immunonutrition studies involving patients undergoing cancer surgery, was the relative homogeneity of the patient group. We had the opportunity to use a large database of gastric cancer patients referred to our institution and to analyze data with a scope and a statistical power that are uncommon for clinical investigations of this type. The homogeneity of our research was also guaranteed by comparable baseline clinical and demographic factors, including nutrition-related and cancer-related variables.

In the present study, early enteral immunonutrition after surgery conferred consistent advantages in overall clinical outcome compared with an isocaloric, isonitrogenous standard enteral postoperative feed. The most important parameters differed significantly in favor of postoperative immunodiets. Overall, infectious complications were reduced, and the anastomotic leak rate of IED group was lower than that of the SEN group. The length of hospital stay was significantly shorter. In contrast, there were no significant differences in the incidence of mortality.

A meta-analysis of 21 randomized trials involving major gastrointestinal surgery, as well as results demonstrated by Zheng et al. and Heyland et al.[19,21,31,33,51] also concluded that immunonutrition decreased anastomotic leakage, morbidity, and hospital stay, but not mortality rates.

Some authors believe that early postoperative immunonutrition is not able to prevent the immunosuppression produced immediately after surgery, advocating the initiation of nutrition before the surgical procedure.[27] Our study first describes the effect of postoperative immunodiet on infectious complications divided into "early" and "late" in relation to their occurrence. Interestingly, in the "late postoperative period" a lower complication rate was registered in immunoenriched diet group compared with standard enteral nutrition diet group. The fact that no differences were observed in the "early" period groups could represent a clearly favorable effect of early postoperative immunonutrition.

Our study showed that the duration of SIRS in the IED group was significantly shorter than that in the SEN group. According to Okamoto et al.[1,17,52] and clinical trials, the preoperative provision of immunomodulatory nutrients promotes the restoration of normal homeostasis postoperatively and the reduction of proinflammatory mediators involved in the development of SIRS after an acute-phase response post total gastrectomy for gastric cancer. These results are similar to our data obtained with early postoperative immunodiet, strengthening the clinical value of the immunonutrition on improving the status of SIRS in patients with gastric cancer.

The results on cellular immunity showed that the postoperative $CD4^+$ T-cell counts decreased in both groups, but the reduction in the IED group was significantly higher compared with the SND group, with no other significant difference observed on PrOD and postoperative day 7 between the 2 groups. It is likely that postoperative immunomodulation effectively improves the postoperative immune and inflammatory responses after gastric surgery by modulation of immune function, as reported by Okamoto et al. and Braga et al.[1,52]

In conclusion, our results clearly show that administration of an enteral nutrition formula supplemented with arginine, omega-3 fatty acids, and RNA in the early postoperative period to patients undergoing total gastrectomy for gastric neoplasm significantly improves clinical outcomes, as evidenced by a substantial reduction in anastomosis healing failures and in postoperative infections by improving the cellular immunity. In order to confirm our findings, larger, prospective, randomized, and double-blind studies are needed.

DISCLOSURE All authors have no conflict of interest or financial ties to disclose.

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