ORIGINAL ARTICLE

Nutritional Approach in Malnourished Surgical Patients

A Prospective Randomized Study

Marco Braga, MD; Luca Gianotti, MD, ScD; Luca Nespoli, MD; Giovanni Radaelli, PhD; Valerio Di Carlo, MD

Hypothesis: Perioperative administration of a supplemented enteral formula may decrease postoperative morbidity.

Design: Randomized clinical trial.

Setting: Department of surgery at a university hospital.

Patients: One hundred ninety-six registered malnourished patients (weight loss ≥10%) who were candidates for major elective surgery for malignancy of the gastrointestinal tract.

Intervention: After randomization (n=150), one group received postoperative enteral feeding with a standard diet within 12 hours of surgery (control group; n=50). Another group orally received 1 L/d for 7 consecutive days of a liquid diet enriched with arginine, ω-3 fatty acids, and RNA (preoperative group; n=50). After surgery, patients were given the same standard enteral formula as the control group. A third group orally received 1 L/d for 7 consecutive days of the enriched liquid diet. After surgery, patients were given enteral feeding with the same enriched formula (perioperative group; n=50).

Main Outcome Measures: Postoperative complications and length of hospital stay.

Results: The 3 groups were comparable for baseline demographics, biochemical markers, comorbidity factors, and surgical variables. The intent-to-treat analysis showed that the total number of patients with complications was 24 in the control group, 14 in the preoperative group, and 9 in the perioperative group ($P=.02$, control group vs perioperative group). Postoperative length of stay was significantly shorter in the preoperative (13.2 days) and perioperative (12.0 days) groups than in the control group (15.3 days) ($P=.01$ and $P=.001$, respectively, vs the control group).

Conclusion: Perioperative immunonutrition seems to be the best approach to support malnourished patients with cancer.

Arch Surg. 2002;137:174-180

PROTEIN ENERGY malnutrition is recognized as an important risk factor for the occurrence of postoperative complications.[1-3] Thus, artificial nutritional support has been proposed as an essential part of perioperative care of malnourished surgical patients.[4-6] Feeding enterally rather than parenterally may improve outcome, particularly in malnourished patients who undergo major surgery for a neoplasm.[7-12]

Moreover, administration of standard enteral diets supplemented with arginine, ω-3 fatty acids, glutamine, and other key nutritional substrates (immunonutrition) modulates immune and inflammatory responses and gut function.[13,14]

Results of 2 randomized, double-blind trials[15,16] consistently indicated that perioperative (before and after surgery) administration of immunoenhancing diets could significantly improve several outcome variables, but none of these studies were designed with separate randomization according to the nutritional status of the patients. Results of a post-hoc analysis[16] suggested that the positive effects of immunonutrition were more pronounced in a subgroup of malnourished patients. Another finding was that patients receiving only preoperative immunonutrition, because of noncompliance with postoperative immunonutrition, also had a significant reduction in complications (M.B., L.G., G.R., et al, unpublished data, 1999). These data suggested that the simple preoperative approach could be sufficient to improve outcome.

Therefore, this study was designed with the primary end point of establishing in a prospective fashion whether administration of perioperative immunonutrition could reduce the rate of post--

From the Department of Surgery, San Raffaele University (Drs Braga, Gianotti, Nespoli, and Di Carlo), and the Department of Informative Systems and Statistics, University of Milan (Dr Radaelli), Milan, Italy.

PATIENTS AND METHODS

This was a randomized clinical trial conducted by a single institution (San Raffaele Hospital, Milan, Italy) between September 1, 1998, and December 31, 2000.

Inclusion and exclusion criteria are summarized in **Table 1**. Patients had to meet all 3 inclusion criteria to be registered. After applying the exclusion criteria, patients were allocated by computer-generated individual random numbers into 3 arms. Eligible patients were required to sign a written informed consent form after the details of the protocol were fully explained. The protocol was approved by the ethical committee of San Raffaele Hospital.

Before surgery, one group drank 1 L of a supplemented liquid diet (Oral Impact; Novartis Consumer Health, Bern, Switzerland) per day for 7 consecutive days. After surgery, patients continued to be fed enterally with the same supplemented formula (perioperative group).

Before surgery, another group drank 1 L of a supplemented liquid diet (Oral Impact) per day for 7 consecutive days. After surgery, patients were given a standard enteral formula (preoperative group).

The third group received only postoperative enteral feeding with a standard diet (control group).

The standard and enriched diets contained the same amounts of energy and nitrogen (**Table 2**). Regardless the type of diet, in all 3 groups, postoperative enteral nutrition was administered within 12 hours of surgery via a feeding catheter jejunostomy or a nasojejunal feeding tube. Enteral flow was controlled by using a peristaltic infusion pump. The initial rate of 10 mL/h was progressively increased 20 mL/h per day until reaching the full nutritional goal (28 kcal/kg per day). Enteral infusion was continued until patients resumed adequate oral food intake (approximately 50% of the basal energy requirement).

All patients were advised to consume regular food as desired before surgery. In the preoperative and perioperative groups, presurgical oral supplementation with the enriched formula was given as outpatient therapy. Patients were also asked to register the daily amount of the preoperative supplement consumed. Hospital admission was scheduled for all patients 2 days before surgery.

Eight days before surgery, the following baseline variables were determined in all patients: body weight, degree of weight loss (with respect to usual body weight in the previous 6 months), performance status according to Karnofsky score, hemoglobin level, plasma level of total protein, albumin level, retinol binding protein level, prealbumin level, total circulating lymphocyte count, creatinine level, and arginine plasma level. The arginine level was also determined 1 day before surgery. Comorbidity factors, as measured by the American Society of Anesthesiologists score, were also recorded in all patients.

Type of surgery, duration of surgery, operative blood loss, and rate and amount of homologous blood transfused were registered. The decision to give homologous blood was based on the perioperative hemoglobin level (<8 g/dL) or the clinical condition of the patient.

Intestinal washout with an isosmotic solution (3 L) was carried out the day before surgery in patients undergoing colorectal surgery. The evening before and the morning of surgery, patients were also treated with enemas. These patients received antibiotic prophylaxis in a single intravenous dose (2 g of cefotetan disodium) 30 minutes before surgery. Candidates for gastric, esophageal, or pancreatic surgery were treated with intestinal washout (1 L) the day before surgery and with antibiotic prophylaxis in a single intravenous dose (2 g of cefazolin sodium) 30 minutes before surgery. A second dose of the antibiotic was given if the surgery lasted longer than 4 hours. Deep-vein thrombosis prophylaxis was carried out daily using low-molecular-weight heparin (50 IU/kg).

Adverse effects of postoperative enteral feeding, such as abdominal cramping and distension, diarrhea (defined as >3 liquid stools per day), and vomiting, were evaluated in all patients, as was the time from canalization to gas and bowel movement.

Patients were defined as nontolerant to postoperative feeding if they were unable to tolerate a minimum diet infusion of 800 mL/d by postoperative day 4.

Trained members of the surgical staff who were not involved in the study registered the postoperative complications (definitions are given in **Table 3**). They also decided independently the day of hospital discharge, the indication, and the duration of antibiotic therapy in the postoperative course and the first day of oral food resumption. Total parenteral nutrition was given to patients who were nontolerant of enteral nutrition.

Death, anastomotic leak, relaparotomy, complications requiring transfer of the patient to the intensive care unit, and percutaneous drainage of a deep abscess using interventional radiologic techniques were defined as major complications. Follow-up for infectious and noninfectious complications was carried out for 30 days after hospital discharge via office visits.

STATISTICAL ANALYSIS

It was assumed that postoperative complications would occur in approximately 40% of eligible control patients.[7,16] A reduction in the incidence to 20% would indicate the efficacy of perioperative immunonutrition treatment. With a targeted maximum of 50 individuals in each group, we had approximately 80% power to detect such a reduction at $\alpha = .05$.

All patients were analyzed on an intent-to-treat basis. Descriptive results are given as mean (SD) or number (percentage) of observations. One-way analysis of variance and the Kruskal-Wallis test (for nonnormally distributed data, ie, operative time, operative blood loss, length of stay, resumption of oral food intake, duration of antibiotic therapy) were used to compare continuous variables among groups. Post-hoc multiple comparisons were performed using the Bonferroni correction. The χ^2 test (with Yates correction if there were cells with <10 observations) and the Fisher exact test were used to compare discrete variables. All P values are 2-sided, and significance was set at $P<.05$. A statistical software program (SPSS version 8.0 for Windows; SPSS Inc, Chicago, Ill) was used for statistical analysis.

operative complications and the length of postoperative hospital stay compared with administration of standard enteral formulas in a homogeneous group of patients defined a priori as malnourished. Furthermore, we evaluated, in the policy of cost minimization, whether the simple preoperative administration of immunonutrition could be as effective as the perioperative approach.

RESULTS

During the study, 196 patients were observed: 46 were excluded and 150 were eligible and entered by randomization into the control group (n=50), the preoperative group (n=50), or the perioperative group (n=50). All eligible patients were analyzed on an intent-to-treat basis (**Figure**).

Table 1. Inclusion and Exclusion Criteria

Inclusion criteria
Weight loss ≥10% (with respect to usual body weight) in the past 6 mo
Histologically proven neoplasm of the gastrointestinal tract
Scheduled for major elective surgery
Exclusion criteria
Respiratory tract dysfunction (arterial Pa_{O_2} <70 mm Hg)
Cardiac dysfunction (New York Heart Class >3, stroke history)
Karnofsky score <60
Hepatic dysfunction (Child-Pugh score >2, portal hypertension)
Ongoing infection
Renal dysfunction (serum creatinine level >3 mg/dL [>265 µmol/L], hemodialysis)
Immune disorder (neoadjuvant radiochemotherapy, neutrophil level <2000/µL, hypoimmunoglobulinemia)
Pregnancy
Age <18 y

Table 2. Composition of the Diets

Component	Standard Diet	Supplemented Diet
Proteins, g/L	56*	56*
Lipids, g/L	28	28
ω-6 Fatty acids, g/L	24.1	8.3
ω-3 Fatty acids, g/L	0	10.5
Carbohydrates, g/L	134	134
Total energy, kcal/L	1010	1010

*The supplemented diet contains 12.5 g of arginine. In the standard diet, arginine was substituted with an isonitrogenous mix of glycine, serine, alanine, and proline.

The mean preoperative intake of the oral supplementation was 910 mL/d, with no difference between the preoperative and perioperative groups. **Table 4** lists the preoperative (day –8) characteristics and the comorbidity factors of the eligible participants. The 3 study arms were well-balanced for all variables. Mean weight loss was 13%. Mean serum levels of total protein, albumin, prealbumin, and retinol binding protein were below the reference range in all groups. The arginine plasma level was similar 8 days before surgery in all groups, whereas 1 day before surgery the level was 1.15 mg/dL in the control group, 1.64 mg/dL in the preoperative group, and 1.69 mg/dL in the perioperative group (P=.03). The 3 groups were comparable for surgical variables (**Table 5**). Most patients underwent upper gastrointestinal tract operations.

Outcome variables are given in **Table 6**. The total number of patients who developed postoperative complications was significantly lower in the perioperative group than in the control group (P=.02). Moreover, the number of patients with complications was 9 (18%) of 50 in the perioperative group vs 14 (28%) of 50 in the preoperative group (50% relative reduction), but this difference did not reach statistical significance (P=.34). Also, comparing the preoperative and control groups, a substantial reduction in complications was observed (28% vs 42%; P=.21). Mean length of postoperative hospital stay was significantly shorter in the preoperative (P=.01) and perioperative (P=.001) groups than in the control group.

Table 7 gives the complications in each group. Considering infectious morbidity, respiratory tract and wound infections were the most frequent, with a lower incidence in the groups receiving immunonutrition than in controls. Among major complications, anastomotic leak seemed to be the most frequent, with a similar trend toward reduction in both groups receiving the enriched diet.

The duration of antibiotic therapy needed to treat postoperative infections was 6.1 (1.7) days in the perioperative group vs 5.8 (3.5) days in the preoperative group and 10.2 (6.3) days in the control group.

Table 3. Definitions of Complications

Complication	Definition
Wound infection	Any redness or tenderness of the surgical wound, with discharge of pus
Abdominal abscess	Deep collection of pus
Pulmonary tract infection	Abnormal chest radiograph, with fever (temperature >38°C) and white blood cell count $>12\times10^3$/µL and positive sputum or bronchoalveolar lavage
Urinary tract infection	$>10^7$ Microorganisms per 1 mL of urine
Bacteremia	Two consecutive positive blood cultures without shock
Wound dehiscence	Any dehiscence of the fascia >3 cm
Bleeding	Necessity of blood transfusion (≥2 U)
Anastomotic leak	Any dehiscence with clinical or radiologic evidence
Respiratory tract failure	Presence of dyspnea and respiratory rate >35 breaths/min or Pa_{O_2} <70 mm Hg
Circulatory insufficiency	Unstable blood pressure requiring use of extra fluids or cardiac stimulants
Renal dysfunction	Increased serum urea or creatinine level (50% above baseline)
Renal failure	Necessity of hemodialysis
Hepatic dysfunction	Increased serum bilirubin or hepatic enzyme level (50% above baseline)
Pancreatic fistula	Daily output of fluid >10 mL from surgical drainage, with an amylase level 5 times higher than the serum concentration
Delayed gastric emptying	Necessity for nasogastric suction for ≥8 d after surgery
Multiple organ dysfunction syndrome	A state of physiological derangement in which organ function is not capable of maintaining homeostasis

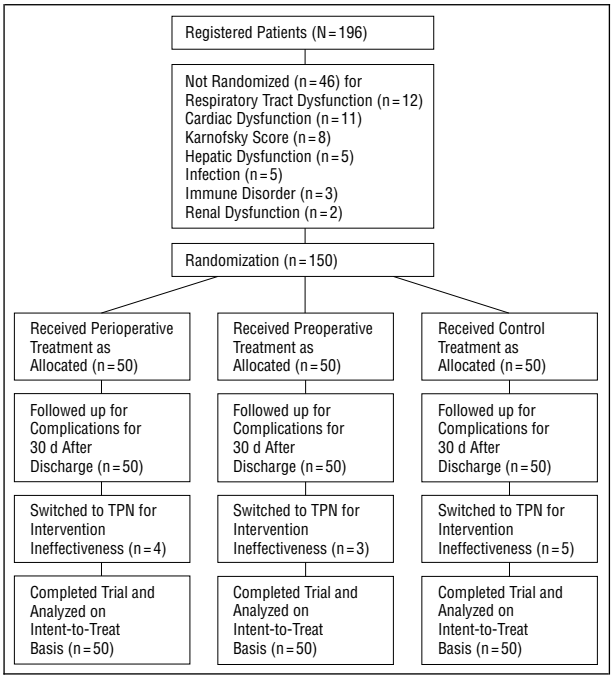

Diagram of the study according to CONSORT (Consolidated Standards of Reporting Trials) statement. TPN indicates total parenteral nutrition.

One hundred four patients (69%) did not experience any adverse effects related to postoperative enteral nutrition. Abdominal cramps or distension were observed in 29 patients (19%), diarrhea in 13 (9%), and vomiting in 4 (3%). The rate of gastrointestinal tract adverse effects was similar in the 3 groups. Because most adverse effects were controlled by the temporary interruption or reduction of the jejunal infusion, overall the nutritional goal was achieved in 138 patients (92%). Twelve patients (8%) had to be switched to total parenteral nutrition for intolerance (5 patients in the control group, 3 in the preoperative group, and 4 in the perioperative group).

Recovery of bowel function as measured by canalization to gas and feces occurred after 3.5 (1.7) and 5.2 (2.1) days, respectively, without any substantial difference among groups. Patients recovered adequate oral food intake 9.8 (5.4) days after surgery in the control group, 8.2 (2.3) days in the perioperative group, and 8.4 (3.6) days in the preoperative group.

Between surgery and hospital discharge, patients lost an additional 3.1% of their body weight. The value was similar among groups.

COMMENT

Malnutrition in patients who are candidates for major surgery is a considerable problem for the surgeon because it represents a risk factor for postoperative morbidity and mortality.[1-3] Cancer-bearing patients may have additional protein energy depletion due to the occurrence of cachexia.[17] Despite extensive research in the field of clinical nutrition,[18] indisputable results on which to base rational nutritional support in malnourished surgical patients are sparse.

A recent consensus statement[18] concluded that malnourished patients are candidates for preoperative artificial nutritional support. This support could reduce the rate of postoperative complications by approximately 10%. These general conclusions have several potential flaws: (1) in the trials analyzed, malnutrition was defined by a multitude of different scores and threshold values for weight loss and serum protein; (2) the study design was rarely a priori dedicated to malnourished patients; (3) enrolled patients were often heterogeneous for the primary diagnosis; (4) the quantity of calories was, in most cases, excessive compared with current standards; and (5) the type of nutrients and the presence of lipids were frequently uncontrolled. These considerations made the comparison among trial results puzzling and the conclusions difficult to be applied in clinical practice. Moreover, nutritional support, with the suggested modalities, requires preoperative hospitalization for at least 7 to 10 days, with an obvious increase in sanitary costs. Another reason for skepticism is that severe malnutrition (the only condition that benefits from preoperative parenteral feeding)[19] is often an indirect sign of ad-

Table 4. Preoperative Characteristics and Comorbidity Factors of 150 Participants*

Variable	Control Group (n = 50)	Preoperative Group (n = 50)	Perioperative Group (n = 50)
Age, y	65.5 (12.4)	65.9 (12.6)	64.1 (12.8)
Sex, M:F, No.	28:22	30:20	26:24
Body weight, kg	59.8 (10.1)	60.2 (9.2)	58.7 (8.8)
Weight loss, %	13.1 (3.6)	12.9 (3.3)	13.3 (4.1)
American Society of Anesthesiologists score	2.3 (1.7)	2.4 (1.5)	2.6 (1.8)
Karnofsky score	81 (13)	82 (8)	78 (14)
Hemoglobin, g/dL	11.8 (1.6)	11.9 (1.7)	11.7 (1.9)
Total proteins, g/dL	6.3 (0.7)	6.2 (0.7)	6.4 (0.5)
Albumin, g/dL	3.5 (0.8)	3.4 (0.6)	3.4 (0.8)
Prealbumin, g/dL	1.8 (1.1)	1.7 (0.9)	2.0 (1.0)
Retinal binding protein, g/L	0.032 (0.016)	0.033 (0.018)	0.034 (0.019)
Total lymphocyte count/μL	1510 (530)	1470 (560)	1490 (650)
Creatinine, mg/dL†	0.77 (0.23)	0.72 (0.19)	0.73 (0.12)
Arginine, mg/dL‡	1.12 (0.15)	1.09 (0.17)	1.11 (0.18)

*Data are given as mean (SD), except where indicated otherwise.
†To convert creatinine from milligrams per deciliter to the SI unit micromoles per liter, multiply milligrams per deciliter by 88.4.
‡To convert arginine from milligrams per deciliter to the SI unit micromoles per liter, multiply milligrams per deciliter by 57.4.

Table 5. Surgical Variables in 150 Participants

Variable	Control Group (n = 50)	Preoperative Group (n = 50)	Perioperative Group (n = 50)
Gastric resection, No.	19	19	18
Pancreatic resection, No.	18	20	21
Colorectal resection, No.	11	8	10
Esophageal resection, No.	2	3	1
Operative time mean (SD), min	244 (110)	258 (90)	263 (97)
Operative blood loss, mean (SD), mL	452 (330)	485 (312)	493 (291)
Transfused patients, No.	17	16	18
Transfusion, mean (SD), mL	555 (310)	570 (255)	480 (190)

Table 6. Outcome Variables

Variable	Control Group (n = 50)	Preoperative Group (n = 50)	Perioperative Group (n = 50)
Patients with major complications, No.	12	9	6
Patients with infectious complications, No.	12	8	5
Patients with noninfectious complications, No.	11	10	6
Patients with complications, total No.	21	14	9*
Length of hospital stay, mean (SD), d	15.3 (4.1)	13.2 (3.5)†	12.0 (3.8)‡

*P = .02 vs the control group.
†P = .01 vs the control group.
‡P = .04 vs the preoperative group and P = .001 vs the control group.

Table 7. Major and Minor Complications in 150 Patients

	Control Group (n = 50)	Preoperative Group (n = 50)	Perioperative Group (n = 50)
Major Complications			
Death	2	1	0
Anastomotic leak	5	3	3
Reason for transfer to intensive care unit			
Respiratory tract failure	2	1	1
Circulatory insufficiency	0	1	0
Multiple organ dysfunction syndrome	0	0	1
Reason for relaparotomy			
Abdominal abscess	1	1	0
Bleeding	1	0	1
Intestinal obstruction	0	1	0
Percutaneous drainage of an abdominal abscess	0	1	1
Minor Complications			
Infectious			
Respiratory tract	6	3	3
Wound	4	2	2
Urinary tract	2	2	1
Bacteremia	2	1	0
Noninfectious			
Pleural effusion/atelectasis	3	2	2
Delayed gastric emptying*	2	3	1
Pancreatic fistula	1	2	1
Systemic inflammatory response syndrome	2	2	1
Bleeding	2	0	0
Deep vein thrombosis	1	0	0
Arrythmia	1	2	1
Renal dysfunction	0	1	0

*Occurring in 5 patients with pancreaticoduodenectomy and in 1 with abdominoperineal amputation of the rectum.

vanced neoplastic disease (unresectable tumor, metastatic spread, peritoneal carcinosis, etc), which usually makes patients unsuitable for a surgical approach. Therefore, the cost-effectiveness of this nutritional treatment may be limited.[20]

Results of recent studies strongly suggest that in malnourished patients, postoperative enteral feeding with standard feeds should be preferred to parenteral nutrition. In fact, surgical patients fed enterally had an improved outcome compared with patients treated parenterally,[7-12] and the nutrition-related sanitary costs are substantially reduced when using the enteral route.[7,21-23] Thus, we believe that postoperative enteral nutrition with a standard diet could be considered the reference treatment. In the present study, we did not include an unfed group because it was considered unethical to restrain such patients from any support.

In the past decade, research in clinical nutrition focused on the addition of key substrates (arginine, ω-3 fatty acids, glutamine, RNA, etc) to standard formulas. Two meta-analyses[24,25] showed that in surgical patients, postoperative use of enteral immunonutrition seems to improve outcome compared with standard formulas. Nevertheless, by analyzing singularly the major studies,[26-30] the results were conflicting. In fact, the positive findings reported by Daly et al[26,27] were partially confirmed by others.[28-30] Postoperative treatment is conceptually limited because the amount of key substrates given in the first days after surgery is little and therefore may be insufficient for an efficacious modulation of the immune and inflammatory responses after surgery.[31-34] As any other substance with supposed pharmacological action, immunonutrients should reach suitable tissue and plasma concentrations to be active. Thus, a different approach was tested to anticipate the provision of immunonutrients before surgery to obtain high levels at the time of surgical stress, when the depression of the host response is maximal.

Phase 2 clinical trials[35-37] showed that perioperative treatment (before and after surgery) with an enteral diet enriched with arginine, ω-3 fatty acids, and RNA significantly prevented early postoperative impairment of the host defense mechanisms, controlled the overwhelming inflammatory reaction, improved intestinal microperfusion and postoperative gut mucosal oxygen metabolism, and modulated the metabolic response favoring the synthesis of constitutive proteins instead of acute-phase proteins.

The impact of perioperative administration of immunoenhancing diets was tested subsequently in phase 3 double-blind trials to address whether the advantages listed in the previous paragraph on surrogate end points could translate into true outcome benefits. Senkal and colleagues[15] showed that patients receiving enteral immunonutrition had significantly fewer infections than the control group (14 vs 27). We[16] reported that in the intent-to-treat analysis, the overall rate of postoperative infectious complications was 14% in the supplemented group and 30% in the control group (P = .009), and length of hospital stay was also shorter in the supplemented group

($P=.01$). Furthermore, our data suggested that perioperative immunonutrition is efficacious regardless of the baseline nutritional status of the patients. In fact, the rate of complication in well-nourished patients was 10% (6/63) in the supplemented group vs 27% (14/68) in the control group ($P=.05$). In a subgroup of malnourished patients, the rate of complication was 14% (3/22) in the supplemented group vs 39% (7/18) in the control group ($P=.05$).

Yet, these studies were not originally designed to randomize patients by their nutritional status. To overcome this bias, we designed a prospective study to investigate the effect of perioperative immunonutrition on outcome in patients a priori homogeneous for nutritional status. In the present trial, we also included a group receiving only preoperative immunonutrition because previous results (M.B., L.G., G.R., et al, unpublished data, 1999) suggested that patients receiving only preoperative immunonutrition because noncompliant with postoperative immunonutrition had a significant reduction in complications. This suggested that the simple preoperative approach could be sufficient to improve outcome. Moreover, in the light of cost-minimization policy, the restriction to preoperative treatment only may save approximately $90 to $180 per treated patient.[15,38]

The results of the present trial are consistent with those of the previous subset analysis and confirm that perioperative treatment with immunonutrition may significantly decrease the postoperative morbidity rate in malnourished patients. In contrast, the expected equivalence between perioperative and preoperative immunonutrition was not achieved. This may be explained by the fact that malnourished patients, beside having energy and nitrogen needs, have marked impairment of the immune response, and, thus, prolonged and increased administration of key nutrients is required. This speculation is consistent with recent data[39] suggesting instead that in well-nourished patients, the simple provision of immunonutrients before surgery was sufficient to improve outcome.

The present data showed a clear trend on the incidence of postoperative complications according to the type of nutrition strategy. In particular, a progressive effect was noted, with perioperative immunonutrition giving the best outcome, postoperative standard formula the worst results, and preoperative immunonutrition intermediate results. Thus, a dose-response effect of key nutrients on the occurrence of complications may be hypothesized.

The 2 groups supplemented with the enriched formula received more energy and proteins than the control group before surgery. However, the better outcome in the groups receiving immunonutrition should not be attributed to the differences in preoperative energy and nitrogen intake compared with the control group because it has been shown previously that when isoenergetic and isonitrogenous preoperative load was used, the results were still in favor of immunonutrition.[15,16] This allows us to speculate that the key factor for improved outcome was the provision of immune-enhancing substrates rather than the simple provision of energy and proteins.

In the present study, the incidence of infection was not significantly different among groups. Yet, patients receiving the supplemented diet required a shorter duration of antibiotic therapy to treat infectious complications. These data may be interpreted as the result of the therapeutic combination of drugs and a more efficient host response on the process of bacterial clearance. Also, it may be hypothesized that the reduction in the postoperative infectious morbidity rate in the supplemented groups is related to improved gut oxygen metabolism and tension already reported in patients perioperatively supplemented with immunonutrition.[35] This may result in advantages on intestinal barrier function and subsequent decreased bacterial translocation that, coupled with malnutrition, may become clinically relevant.[40]

This study was not designed to address treatment and complication costs. Nevertheless, the health care resources saved by the marked reduction in the morbidity rate by using perioperative immunonutrition may largely outnumber the additional costs of the supplemented diet.[15,38]

In conclusion, the present trial is the first, to our knowledge, to report that in a selected population of malnourished patients with cancer undergoing major elective surgery, the administration of key substrates was beneficial to outcome. Administration of the supplemented diet before and after surgery seemed to be the best strategy to reduce complications and length of hospital stay.

The diets were provided by Novartis Consumer Health.

Corresponding author and reprints: Luca Gianotti, MD, ScD, Department of Surgery (Chirurgia 3) San Gerardo Hospital, Via Donizetti 106, 20052 Monza (MI), Italy (e-mail: luca.gianotti@unimib.it).

REFERENCES

1. Mullen JL. Consequences of malnutrition in the surgical patient. *Surg Clin North Am.* 1981;61:465-487.
2. Gianotti L, Braga M, Radaelli G, et al. Lack of improvement of prognostic performance of weight loss when combined with other nutritional parameters. *Nutrition.* 1995;11:12-16.
3. Mora RJF. Malnutrition: organ and functional consequences. *Word J Surg.* 1999; 23:530-535.
4. ASPEN Board of Directors. Guidelines and standards. *JPEN J Parenter Enteral Nutr.* 1995;19:1-2.
5. Società Italiana di Nutrizione Parenterale ed Enterale. Linee guida per l'impiego della nutrizione artificiale nei pazienti adulti ospedalizzati. *Riv Ital Nutr Parenter Enteral.* 1995;13(suppl 2):S2-S7.
6. French-Speaking Society for Parenteral and Enteral Nutrition. Perioperative artificial nutrition in elective adult surgery. *Clin Nutr.* 1996;15:223-229.
7. Braga M, Gianotti L, Gentilini O, Parisi V, Salis C, Di Carlo V. Early postoperative enteral nutrition improves gut oxygenation and reduces costs compared with total parenteral nutrition. *Crit Care Med.* 2001;29:242-248.
8. Bozzetti F, Braga M, Gianotti L, et al. Postoperative enteral versus parenteral nutrition in malnourished patients with gastrointestinal cancer: a randomized multicenter trial. *Lancet.* 2001;358:1487-1492.
9. Beier-Holgersen R, Boesby S. Influence of postoperative enteral nutrition on postsurgical infections. *Gut.* 1996;39:833-835.
10. Sand J, Luostarinen M, Matikainen M. Enteral or parenteral feeding after total gastrectomy: prospective randomized pilot study. *Eur J Surg.* 1997;163:761-766.
11. Carr CS, Ling E, Boulos P, Singer M. Randomised trial of safety and efficacy of immediate postoperative enteral feeding in patients undergoing gastrointestinal resection. *BMJ.* 1996;312:869-871.
12. Moore FA, Feliciano DV, Andrassy RJ, et al. Early enteral feeding, compared with parenteral, reduces postoperative septic complications: the results of a meta-analysis. *Ann Surg.* 1992;216:172-183.
13. Gianotti L, Gentilini O, Braga M. Enteral nutrition with supplemented arginine, glutamine, RNA, and omega-3 fatty acids. *Curr Opt Crit Care.* 1998;4:263-268.
14. Hall JC, Heel K, McCauley R. Glutamine. *Br J Surg.* 1996;83:305-312.

15. Senkal M, Zumtobel V, Bauer K-H, et al. Outcome and cost-effectiveness of perioperative enteral immunonutrition in patients undergoing elective upper gastrointestinal tract surgery. *Arch Surg.* 1999;134:1309-1316.
16. Braga M, Gianotti L, Radaelli G, et al. Perioperative immunonutrition in patients undergoing cancer surgery: results of a randomized double-blind phase 3 trial. *Arch Surg.* 1999;134:428-433.
17. Gianotti L, Gentilini O, Braga M. Nutrition in surgical oncology. In: Mason JB, Nitenberg G, eds. *Cancer & Nutrition: Prevention and Treatment.* Basel, Switzerland: S Karger AG; 2000:239-254.
18. Klein S, Kinney J, Jeejeebhoy K, et al. Nutritional support in clinical practice: review of the published data and recommendation for future research directions. *JPEN J Parenter Enteral Nutr.* 1997;21:133-156.
19. Veteran Affairs Total Parenteral Nutrition Cooperative Study Group. Perioperative total parenteral nutrition in surgical patients. *N Engl J Med.* 1991;325:525-532.
20. Eisenberg JM, Glick HA, Buzby GP, Kinosian B, Williford WO. Does perioperative total parenteral nutrition reduce medical costs? *JPEN J Parenter Enteral Nutr.* 1993;17:199-200.
21. Salis C, Paccagnella A, Vannucci A, Faraguna D, Michieletto F. Italian multicentric study of the resources employed in artificial nutrition in hospitalized patients. *Riv Ital Nutr Parenter Enteral.* 1998;16:14-24.
22. Wicks C, Somasuydaram S, Bjarnason I, et al. Comparison of enteral feeding and total parenteral nutrition after liver transplantation. *Lancet.* 1994;344:837-840.
23. Hedberg AM, Lairson DR, Aday LA, et al. Economic implications of an early postoperative enteral feeding protocol. *J Am Diet Assoc.* 1999;99:802-807.
24. Beale RJ, Bryg DJ, Bihari DJ. Immunonutrition in the critically ill: a systematic review of clinical outcome. *Crit Care Med.* 1999;27:2799-2805.
25. Heys S, Walker LG, Smith I, et al. Enteral nutrition supplementation with key nutrients in patients with critical illness and cancer: a meta-analysis of randomized controlled clinical trials. *Ann Surg.* 1999;229:467-477.
26. Daly JM, Lieberman MD, Goldfine J, et al. Enteral nutrition with supplemental arginine, RNA, and omega 3 fatty acids in patients after operation: immunologic, metabolic and clinical outcome. *Surgery.* 1992;112:56-67.
27. Daly JM, Weintraub FN, Shou J, Rosato EF, Lucia M. Enteral nutrition during multimodality therapy in upper gastrointestinal cancer patients. *Ann Surg.* 1995; 221:327-338.
28. Senkal M, Mumme A, Eickhoff U, et al. Early postoperative immunonutrition: clinical outcome and cost-comparison analysis in surgical patients. *Crit Care Med.* 1997;25:1489-1496.
29. Gianotti L, Braga M, Vignali A, et al. Effect of route of delivery and formulation of postoperative nutritional support in patients undergoing major operations for malignant neoplasm. *Arch Surg.* 1997;132:1222-1230.
30. Heslin MJ, Latkany L, Leung D, et al. A prospective randomized trial of early enteral feeding after resection of upper gastrointestinal malignancy. *Ann Surg.* 1997; 226:567-580.
31. Braga M, Vignali A, Gianotti L, Cestari A, Profili M, Di Carlo V. Immune and nutritional effects of early enteral nutrition after major abdominal operations. *Eur J Surg.* 1996;162:105-112.
32. Kemen M, Senkal M, Homann HH, et al. Early postoperative enteral nutrition with arginine, omega-3 fatty acids and ribonucleic acid–supplemented diet versus placebo in cancer patients: an immunologic evaluation of Impact. *Crit Care Med.* 1995;23:652-659.
33. Senkal M, Kemen M, Homann HH, et al. Modulation of postoperative immune response by enteral nutrition with a diet enriched with arginine, RNA, and omega-3 fatty acids in patients with upper gastrointestinal cancer. *Eur J Surg.* 1995;161: 115-122.
34. Cerra FB, Lehmann S, Kostantinites N, et al. Improvement in immune function in ICU patients by enteral nutrition supplemented with arginine, RNA, and menhaden oil is independent of nitrogen balance. *Nutrition.* 1991;7:193-199.
35. Braga M, Gianotti L, Cestari A, et al. Gut function and immune and inflammatory responses in patients perioperatively fed with supplemented formulas. *Arch Surg.* 1996;131:1257-1265.
36. Gianotti L, Braga M, Fortis C, et al. A prospective randomized clinical trial on perioperative feeding with an arginine, omega-3 fatty acids, and RNA-enriched enteral diet: effect on host response and nutritional status. *JPEN J Parenter Enteral Nutr.* 1999;23:314-320.
37. Wachtler P, Axel R, König W, Bauer H, Kemen M, Köller M. Influence of a preoperative enteral supplementation on functional activities of peripheral leukocytes from patients with major surgery. *Clin Nutr.* 1995;14:275-282.
38. Gianotti L, Braga M, Frei A, Greiner R, Di Carlo V. Health care resources consumed to treat postoperative infections: cost saving by perioperative immunonutrition. *Shock.* 2000;14:325-330.
39. Gianotti L, Braga M, Radaelli G, Nespoli L, Di Carlo V. A prospective randomized trial on pre-operative immunonutrition in well-nourished patients undergoing major surgery for gastrointestinal cancer [abstract]. *Br J Surg.* 2001;88: 1142.
40. Deitch EA, Winterton J, Berg RD. The gut as a portal of entry for bacteremia: role of protein malnutrition. *Ann Surg.* 1987;205:681-692.

IN OTHER AMA JOURNALS

ARCHIVES OF INTERNAL MEDICINE

Environmental and Drug Effects on Patients With Pacemakers and Implantable Cardioverter/Defibrillators: A Practical Guide to Patient Treatment

Nora Goldschlager, MD; Andrew Epstein, MD; Paul Friedman, MD; Eli Gang, MD; Ryszard Krol, MD, PhD; Brian Olshansky, MD; for the North American Society of Pacing and Electrophysiology (NASPE) Practice Guideline Committee

The potential for interaction between pacemakers and implantable cardioverter/defibrillators (ICDs) and the medical and nonmedical environment, and between these devices and certain cardioactive drugs, has been recognized for years. Whereas a number of experimental and clinical studies have been performed to define some of these interactions, in many instances data are sparse and anecdotal clinical experiences form the basis for decision making and recommendations. Nevertheless, given the proliferation of rhythm-management devices in use in the population today, practitioners may find a guide to management of these patients helpful. This management guideline is therefore offered not as an extensive, literature-based review, but as a framework on which to understand specific types of problems that may be encountered in the daily lives of patients who have such implanted devices. (*2001;161:649-655*)

Corresponding author and reprints: Nora Goldschlager, MD, University of California, San Francisco, San Francisco General Hospital, Cardiology Division, Room 5G1, Box 0846, San Francisco, CA 94110.