

Early postoperative enteral nutrition improves gut oxygenation and reduces costs compared with total parenteral nutrition

Marco Braga, MD; Luca Gianotti, MD, ScD; Oreste Gentilini, MD; Valeria Parisi, MD; Carlo Salis, PharmD; Valerio Di Carlo, MD

Objective: To evaluate the potential clinical, metabolic, and economic advantages of enteral nutrition over total parenteral nutrition.

Design: Prospective, randomized clinical trial.

Setting: Department of surgery in a university hospital.

Patients: Two hundred and fifty-seven patients with cancer of the stomach (n = 121), pancreas (n = 110), or esophagus (n = 26) were randomized to receive postoperative total parenteral nutrition (TPN group, n = 131) or early enteral nutrition (EEN group, n = 126). The nutritional goal was 25 kcal/kg/day. The two nutritional formulas were isocaloric and isonitrogenous, and they were continued until oral intake was at least 800 kcal/day.

Measurements: Morbidity, mortality, length of hospital stay, and treatment costs were evaluated in all patients. In 40 consecutive patients, selected nutritional, immunologic and inflammatory variables were studied. Moreover, intestinal oxygen tension was evaluated by micropolarographic implantable probes.

Main Results: The nutritional goal was reached in 100/126 (79.3%) patients in the EEN group and in 128/131 (97.7%) patients

in the TPN group ($p < .001$). In the EEN group, hyperglycemia (serum glucose, >200 mg/dL) was observed in 4.7% of the patients vs. 9.1% in the TPN group ($p = \text{NS}$). Alteration of serum electrolyte levels was 3.9% in the EEN group vs. 13.7% in the TPN group ($p < .01$). No significant difference was found in nutritional, immunologic, and inflammatory variables between the two groups. The overall complication rate was similar (40.4% for TPN vs. 35.7%, for EEN; $p = .52$). No difference was detected for either infectious or noninfectious complications, length of hospital stay, and mortality. From postoperative day 5, intestinal oxygen tension recovered faster in the EEN group than in the TPN group (43 ± 5 mm Hg vs. 31 ± 4 mm Hg at day 7; $p < .001$). EEN was four-fold less expensive than TPN (\$25 vs. \$90.60/day, respectively).

Conclusion: EEN represents a rational alternative to TPN in patients who undergo upper gastrointestinal tract surgery for cancer and who clinically require postoperative artificial nutrition. (Crit Care Med 2001; 29:242-248)

KEY WORDS: nutrition; enteral; parenteral; surgery; cancer; outcome; metabolism; gut; oxygenation; cost

International guidelines propose the use of postoperative artificial nutrition in either undernourished patients or well-nourished subjects when the estimated period of postoperative semistarvation is longer than 10 days (1-3). In such patients, total parenteral nutrition (TPN) is commonly prescribed, although recent reviews suggest that the more physiologic enteral nutrition is feasible and safe after major surgery and trauma (4, 5). Nevertheless, at present, definitive data suggesting that in elective surgical patients early enteral nutrition (EEN) is superior to TPN on outcome variables are lacking. In fact,

only a few small studies have been published on this specific topic (6, 7).

The aim of this study was to evaluate the effect of EEN on the immunometabolic response, the gut oxygenation, and the postoperative complication rate compared with TPN in a large sample of patients undergoing curative operation for cancer of upper gastrointestinal (GI) tract. A cost analysis of the two nutritional regimens was also carried out.

MATERIALS AND METHODS

This study is partially a continuation of a previous experience (8) and includes a total of 257 patients (111 who were also considered in the previous experience and 146 who were consecutively recruited afterward).

Inclusion criterion was the diagnosis of cancer of the upper GI tract, suitable for curative surgery. According to international guidelines, these patients were considered candidates for postoperative nutritional support because they are often undernourished and they are usually unable to recover an

adequate oral intake within 10 days after operation (1-3).

Exclusion criteria were renal (creatinine level >30 mg/dL, hemodialysis), hepatic (ascites, portal hypertension, encephalopathy), cardiac (New York Heart Association class >3), or pulmonary dysfunction (arterial Pao_2 of <70 torr [9.3 kPa]), ongoing infection, neoadjuvant radiochemotherapy, and immune disorders (neutrophil level of $<2.0 \times 10^9/\text{L}$, hypoinmunoglobulinemia). The study protocol was approved by our Institution Ethical Committee. Patients were required to sign a written informed consent form after the details of the study were fully explained.

Three hundred and fourteen patients met the inclusion criteria; 140 patients had gastric cancer, 138 pancreatic cancer, and 36 esophageal cancer.

On admission (baseline), the following variables were recorded in all patients: age, sex, body weight, Karnofsky scale score, hemoglobin, blood glucose, creatinine, serum electrolytes, albumin, prealbumin, retinol-binding protein (RBP), and total lymphocyte count. Blood chemistry was repeated 1 and 8 days after surgery.

From the Department of Surgery (Drs. Braga, Gianotti, Gentilini, Parisi, and Di Carlo), Scientific Institute, S. Raffaele Hospital, Milan; and the Hospital Pharmacy (Dr. Salis), Lodi, Italy.

Address requests for reprints to: Marco Braga, MD, Department of Surgery, Scientific Institute, S. Raffaele Hospital, Via Olgettina 60, 20132 Milan, Italy. E-mail: braga.marco@hsr.it

Copyright © 2001 by Lippincott Williams & Wilkins

Patients who had experienced an involuntary weight loss >10% (with respect to their usual body weight) in the preceding 6 months were defined as malnourished.

All patients received antibiotic prophylaxis with a single dose of intravenous cefazolin disodium (2 g). A second dose of antibiotic was administered if the operation lasted more than 4 hrs. Deep venous thrombosis prophylaxis was carried out with a daily subcutaneous injection of low molecular weight heparin (50 IU/kg).

No patient received preoperative artificial nutrition.

Duration of surgery, operative blood loss, and the rate of transfused patients were also recorded.

In 57 patients, palliative surgery was carried out because of unresectable primary tumor (n = 22) or metastatic disease (n = 35). The remaining 257 patients were randomized (same chance) to receive TPN or EEN. Allocation was concealed, until the primary tumor was resected, by sealed opaque envelope. The randomization sequence was generated from a computer program.

The two nutritional formulas were well balanced for nitrogen, energy, electrolyte, and trace element content (Table 1). Nutritional goal was 25 kcal/kg/day. TPN was started on postoperative day (POD) 1 by giving 50% of the nutritional goal, and, from POD 2, patients received the full regimen. EEN was started 6 hrs after the end of the operation at a 10 mL/hr rate with a progressive increase to reach the full regimen on POD 4. In patients randomized to receive EEN, the diet was infused through either a feeding jejunostomy or a nasojejunal tube.

A catheter-feeding jejunostomy (8-Ch Kangaroo, Sherwood Medical, Tullemore, Ireland) was performed by a modified Witzel technique at the end of surgery before closing the wound. The feeding tube was inserted into the peritoneal cavity through a small incision of the skin of the abdominal wall at the left flank. The third jejunal loop (30 cm aborally from the gastrojejunal anastomosis) was then selected. A single purse-string suture was performed, the intestinal loop was perforated on the anti-mesenteric site, and the catheter inserted into the jejunal lumen and advanced for 30 cm distally. The purse string was closed around the entry site of the catheter. The feeding tube was then tunneled on the serosal site on the jejunum for 5 cm by several interrupted sutures. Finally, the jejunal loop was fixed at the peritoneum of the anterior abdominal wall with four interrupted sutures centered on the catheter entry site. The feeding tube was flushed with 20 ml of saline to check for lumen-free passage and leaking.

A nasojejunal tube was placed into patients who underwent gastrectomy. After the esoph-

agus-jejunal anastomosis was carried out (Roux-en-Y) and just before suturing the abdominal wall, a tungsten-weighted 10-Ch feeding tube (Kangaroo, Sherwood Medical) with the guidewire stylet in the lumen, was inserted by the anesthetist through a nostril and gently pushed down until the surgeon felt the tip at the esophageal hiatus. The tube was passed through the esophagus-jejunal anastomosis under the guide of the surgeon and then manually advanced until the distal tip of the tube was 10 cm aborally from the jejunojunction anastomosis. The anesthetist then removed the stylet while the surgeon kept the tube in place.

Artificial nutrition, either TPN or EEN, was continued until patients achieved an adequate oral food intake (800 kcal/day).

In 40 consecutive patients (20 per group), the following variables were measured on admission (baseline) and 1 and 8 days after surgery: C-reactive protein; T-lymphocyte subsets (CD4, CD8); the degree of phagocytosis of polymorphonuclear cell (PMN), expressed as percentage of PMN in which zymosan particles were detected over 100 PMNs (9).

Plasma samples of 10 ml were divided into five aliquots and frozen at -80°C until tested. Quantitative determination of human interleukin (IL)-6 and IL-2 α receptors, in duplicate for each sample, were performed in microtiter plates using a commercially available enzyme-linked immunoabsorbent assays according to the procedures recommended by the manufacturer (Genzyme Diagnostics, Cambridge, UK). Optical density was determined using a microtiter plate reader (Auto-Reader III, Ortho Diagnostic System, Raritan, NJ) at 450 nm, with a correction wavelength set at 540 or 570 nm. The detection limit of the assay was 0.8 pg/mL for IL-6 and 10 pg/mL for the IL-2 α receptors.

Delayed hypersensitivity response was assessed by using seven recall antigens according to the procedure suggested by the manufacturer (Multitest, Pasteur Merieux, Lyon, France). Two diameters (transversal and longitudinal) of each skin test were measured. The mean diameter of a skin test is defined as the sum of the two diameters. A positive reaction is a mean diameter greater than 2 mm. The score is defined as the sum of all mean diameters of the seven skin tests after 48 hrs from the application. The score is a quantitative value expressed in millimeters. The composite score is calculated as the number of positive skin reactions divided by the sum of the mean diameter of the positive skin reactions. Then, the reciprocal of the composite score is calculated. Using this artifact, higher score indicated better immune response.

In these patients, intestinal tissue oxygen pressure was also assessed, according to Jacobi (10), by a catheter oxygen polarographic mi-

Table 1. Composition of the two nutritional regimens (per 100 mL)

	Parenteral	Enteral
Proteins (g)	4.0	4.1 ^a
Carbohydrates (g)	12.7	14.2
Lipids (g)	5.0	3.5
Linoleic acid	1.30	1.02
α -Linolenic acid	0.10	0.15
Medium-chain triglycerides (g)	0	0.62
Sodium (mg)	80	70
Potassium (mg)	130	135
Chlorine	98	100
Calcium	60	55
Phosphorus	50	55
Magnesium	20	22
Iodine (μ cg)	1.6	1.2
Iron (mg)	0.78	1.10
Zinc (mg)	1.36	1.10
Manganese (μ g)	98	210
Copper (mg)	0.4	1.4
Fluorine (mg)	0.21	0.16
Chromium (μ g)	5.3	4.0
Molybdenum (μ g)	4.9	5.4
Selenium (μ g)	8.5	4.6
Vitamin A (μ g)	55	80
Vitamin B ₁ (mg)	0.18	0.1
Vitamin B ₂ (mg)	0.12	0.1
Vitamin B ₆ (mg)	0.10	0.15
Vitamin B ₁₂ (μ g)	0.20	0.24
Vitamin C (mg)	6	5
Vitamin D ₃ (μ g)	0.10	0.36
Vitamin E (mg)	0.6	0.8
Vitamin K (μ g)	6.2	5.6
Biotin (μ g)	7	10
Folic acid (μ g)	4.6	14.0
Nicotinamide (mg)	2.0	1.4
Pantothenic acid (mg)	0.80	0.43
Osmolarity (mOsm/L)	1185	201
Total calories (kcal)	110	105

^a80% from casein and 20% from soy.

croprobe (type CC1.2 Licox, GMC, Kiel-Miendorf, Germany) inserted through the abdominal wall and then placed into the thickness of the cecum wall during surgery. The probe was sutured to the visceral surface of the cecum and connected to the Licox CMP monitor device (type AC3, GMC) and interfaced with an IBM-compatible personal computer. The data gathered were analyzed by dedicated software (Licox Po₂ computer software, version 2.6e). Oxygen tension was measured starting immediately after laparotomy and ending immediately before suturing the abdominal wall. Moreover, Po₂ was measured daily until POD 7 for 1 hr/day. During monitoring the patients were asked to rest in bed.

Glucose serum concentration greater than 200 mg/dL for two consecutive measurements during artificial nutrition was defined *a priori* as abnormal, thus requiring insulin administration. Diabetic patients (n = 55) were excluded from the analysis. Serum electrolyte abnormalities during nutritional treatment were defined *a priori* as follows: variation of 5% from the lower and upper limit of the

normal range for sodium and chlorine (135 to 148 mmol/L and 98 to 108 mmol/L, respectively) and of 10% for potassium (3.5 to 5.0 mmol/L). These abnormalities were corrected by variation of electrolyte administration or by pharmacologic treatment.

Serum concentration was determined twice a day for glucose (8 am and 8 pm) and once a day for electrolytes (8 am) in both groups.

Postoperative complications were recorded by members of the surgical staff who were not involved in the trial, according to criteria reported in previous studies (8, 11). Microbiological analysis and positive culture proved all infectious complications. The severity of postoperative infections was scored as described by Elebute and Stoner (12).

Major complications were defined as the need of repeat laparotomy, percutaneous drainage of intra-abdominal deep fluid collection by interventional radiology procedures, or complications requiring patient transfer to the intensive care unit.

Abdominal bloating, abdominal cramps, diarrhea (defined as more than three bowel movements per day), vomiting, and displacement of jejunostomy or nasojejunal tubes were considered adverse effects of enteral nutrition. The first bowel movement (gas and feces) after operation was recorded in all patients.

The cost analysis of artificial nutrition was performed by considering the following variables: a) infusion set (catheter, pump, line, dressing); b) tests for monitoring (laboratory, radiologic procedures, microbiology); c) prescriptions (nutritional formulas including vitamins, electrolytes and trace elements); and d) sanitary personnel (physicians, nurses, technicians, pharmacists).

For statistical analysis, the sample size of the groups was determined to detect a 40% reduction in the overall complications in the EEN group, with respect to a complication rate of 40% in the TPN group (8). Assuming a type I error of 0.05 and a power of 0.80, 129 patients in each group were required to show a significant difference. Student's *t*-test was used to compare normally distributed continuous variables and the Mann-Whitney U test to compare abnormally distributed variables (duration of surgery and blood loss). The difference between discrete variables was analyzed by the chi-square test or Fisher's exact test. The analysis of variance for repeated measures or the Friedman's test (when appropriate) were used to compare temporal variations. The level of significance was adjusted for multiple comparisons by the Student-Newman-Keul test. The results are reported as mean \pm SD unless otherwise specified. Statistical calculation was made using the SPSS 7.5 package for Windows (SPSS, Chicago, IL).

RESULTS

The two groups were similar for baseline characteristics and surgical variables (Table 2).

Duration of artificial nutrition was 13.2 ± 4.9 days and 12.8 ± 5.5 days in the TPN and the EEN groups, respectively. In the first postoperative week, the mean energy intake per day was 1632 ± 281 kcal (range, 855 to 2518) in the TPN group vs. 1522 ± 317 kcal (range, 564 to 2420) in the EEN group ($p = .11$). Nutritional goal was achieved within 4 days postoperatively in 128/131 (97.7%) patients in the TPN group, and in 100/126 (79.3%) patients in the EEN group ($p < .001$). Seventy-two patients out of 126 (57.1%) of the EEN group did not experience adverse effects. Abdominal cramps were reported by 14.2% of the patients fed enterally vs. 4.5% of the patients fed parenterally, abdominal distension by 12.6% in the EEN group vs. 5.3% in the TPN group, and diarrhea by 11.1% in the EEN group vs. 3.8% in the TPN group. The symptoms related to early enteral feeding were solved either by temporary discontinuation or reduction of infusion rate. In eight patients (6.3%), a permanent stop of the infusion of enteral diet was necessary because of jejunostomy or nasojejunal tube dislocation ($n = 5$; 4%), emesis ($n = 2$; 1.5%), and aspiration ($n = 1$; 0.8%). These patients were switched to TPN support but, for outcome evaluation, were considered in the EEN group on an intent-to-treat basis. Jejunostomy or nasojejunal tube clogging or occlusion occurred in 11 patients. In all cases, flushing or insertion of a stylet allowed the recovery of function. Mild local skin infection at the jejunostomy entry site was

observed in two patients. Seven patients receiving enteral feeding through the nasojejunal tube had the catheter displaced or inadvertently removed. These events occurred 4 (median) days after operation (range, 1–8). In all patients but two, the tube was replaced (10 cm aborally from the jejunostomy) under radiologic guide.

The first flatus occurred 2.4 ± 1.3 days after surgery in the EEN group and 4.6 ± 2.0 days in the TPN group ($p = .003$), whereas the first bowel movement occurred 4.2 ± 1.6 days after surgery in the EEN group and 6.3 ± 2.1 days in the TPN group ($p = .001$).

The rate of hyperglycemia (serum glucose, >200 mg/dL) was 9.1% in patients fed parenterally and 4.7% in the patients fed enterally ($p = .25$). The occurrence rate of serum electrolyte abnormalities was significantly lower in the EEN group than in the TPN group (3.9% vs. 13.7%, respectively; $p = .01$).

At any time point, no significant differences were found between the two groups in all the nutritional variables, immune function variables, and inflammatory response indices (Tables 3, 4, and 5, respectively). In all patients, serum albumin, prealbumin, and RBP dropped significantly after surgery ($p < .01$) and remained low on POD 8. In both groups, delayed hypersensitivity response and PMN phagocytosis were markedly depressed on both POD 1 and 8, whereas total lymphocytes and CD4/CD8 ratio recovered similarly to baseline values on POD 8. No significant differences were found in the levels of IL-2 α receptors. Both C-reactive protein and IL-6 rose sig-

Table 2. Baseline characteristics of the eligible patients and surgical parameters

	Parenteral (n = 131)	Enteral (n = 126)
Age (yrs)	62.9 ± 12.4	64.1 ± 13.1
Male:female	71:60	68:58
Body weight (kg)	66.8 ± 14.9	65.9 ± 13.7
Malnourished patients (%)	48 (36.6)	43 (34.1)
Karnofsky score	76 ± 13	75 ± 12
Hemoglobin (g/L)	127 ± 15	125 ± 16
Albumin (g/L)	37.1 ± 4.2	37.3 ± 3.9
Surgical procedures		
Pancreaticoduodenectomy (%)	59 (45.0)	51 (40.5)
Gastrectomy (%)	62 (47.3)	59 (46.8)
Esophagectomy (%)	10 (7.7)	16 (12.7)
Operative time (mins)	365 ± 95	380 ± 110
Operative blood loss (mL)	530 ± 310	670 ± 345
Transfused patients (%)	41 (31.2)	38 (30.1)

Values are means \pm SD or number of patients (%).

Table 3. Nutritional variables

	Parenteral (n = 131)	Enteral (n = 126)
Albumin (g/L) (normal range, 35–50)		
Baseline	37.1 ± 4.2	37.3 ± 3.9
POD 1	31.2 ± 3.8 ^a	29.8 ± 3.7 ^a
POD 8	34.2 ± 3.7	33.8 ± 4.3 ^a
Prealbumin (g/L) (normal range, 0.20–0.40)		
Baseline	0.24 ± 0.06	0.26 ± 0.05
POD 1	0.13 ± 0.04 ^a	0.14 ± 0.03 ^a
POD 8	0.17 ± 0.06 ^a	0.18 ± 0.05 ^a
RBP (mg/L) (normal range, 36–58)		
Baseline	42.1 ± 9.3	45.2 ± 10.6
POD 1	27.4 ± 7.5 ^a	26.8 ± 6.4 ^a
POD 8	30.3 ± 9.1 ^a	32.7 ± 10.3 ^a

POD, postoperative day; RBP, retinol-binding protein.

^a*p* < .05 vs. baseline. Data are mean ± sd.

Table 4. Immunologic variables

	Parenteral (n = 20)	Enteral (n = 20)
DHR (composite score) (normal value, >60)		
Baseline	0.76 ± 0.18	0.72 ± 0.15
POD 1	0.42 ± 0.07 ^a	0.37 ± 0.08 ^a
POD 8	0.41 ± 0.10 ^a	0.39 ± 0.12 ^a
PMN phagocytosis (%) (normal value, >40)		
Baseline	45.1 ± 8.1	44.8 ± 6.9
POD 1	31.7 ± 4.2 ^a	31.1 ± 4.8 ^a
POD 8	35.1 ± 6.3 ^a	36.4 ± 5.8 ^a
IL-2 α receptors (pg/mL)		
Baseline	593 ± 91	609 ± 88
POD 1	729 ± 165	763 ± 187
POD 8	711 ± 193	730 ± 184
Total lymphocytes (cell/mm ³) (normal range, 860–4800)		
Baseline	1570 ± 430	1622 ± 546
POD 1	1218 ± 358 ^a	1275 ± 416 ^a
POD 8	1324 ± 315	1348 ± 377
CD4/CD8 ratio (normal value, >1)		
Baseline	2.1 ± 1.3	2.0 ± 1.2
POD 1	1.6 ± 1.4 ^a	1.6 ± 1.5 ^a
POD 8	1.9 ± 1.6	1.8 ± 1.3

DHR, delayed hypersensitivity response; POD, postoperative day; PMN, polymorphonuclear cells; IL, interleukin.

^a*p* < .05 vs. baseline. Data are mean ± sd.

nificantly after surgery, maintaining high levels on POD 8.

Intestinal oxygenation is depicted in Figure 1. Oxygen tension level dropped during the operation and remained similar in the two groups until POD 4. A significant increase in the gut oxygen tension in EEN group was found, starting from POD 5.

Outcome variables are reported in Table 6. No significant differences were detected between the two groups for considered outcomes. Details of complications are summarized in Table 7.

A *post hoc* analysis was finally performed in the subgroup of malnourished

patients. Results are reported in Table 8. A tendency to a lower overall complication rate was noted in the EEN group as compared with the TPN group (37.1% vs. 52.0%; *p* = .23). In particular, the rate of infectious complications was 13.9% in the EEN group and 25.0% in the TPN group (*p* = .33). A significantly shorter length of hospital stay was found in the EEN group (19.8 days) compared with the TPN group (22.6 days; *p* = .042).

The results of the cost analysis are summarized in Figure 2. Mean cost per day of EEN was almost four-fold less than TPN (\$25 vs. \$90.60; *p* < .001) (\$1 = 0.95 Euros). Prescriptions represent 73.2% of the mean daily cost in TPN, and 22% in

Table 5. Variables of inflammatory response

	Parenteral (n = 20)	Enteral (n = 20)
CRP (g/L) (normal value, <8)		
Baseline	9.5 ± 2.4	8.7 ± 3.1
POD 1	117 ± 31 ^a	109 ± 38 ^a
POD 8	63 ± 24 ^a	51 ± 22 ^a
IL-6 (pg/mL)		
Baseline	40.9 ± 6.6	39.7 ± 4.1
POD 1	84.1 ± 28.7 ^a	81.1 ± 32.6 ^a
POD 8	92.6 ± 46.3 ^a	75.5 ± 31.8 ^a

CRP, C-reactive protein; POD, postoperative day; IL-6, interleukin-6.

^a*p* < .05 vs. baseline. Data are mean ± sd.

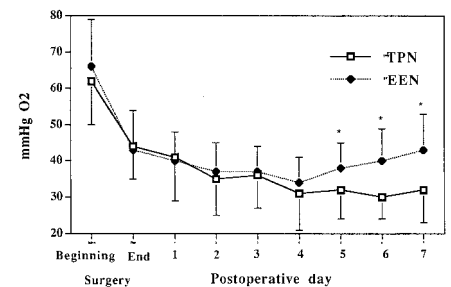


Figure 1. Variations of intestinal oxygen tension during and after surgery (mean ± sd). TPN, total parenteral nutrition; EEN, early enteral nutrition. **p* < .01 vs. TPN.

EEN. In contrast, the costs of the other variables were similar in the two groups.

DISCUSSION

In recent years, EEN has been proposed as the optimal route for nutritional support after operation or trauma because of its claimed advantages over TPN. In fact, in the experimental setting, jejunal infusion of nutrients prevents adverse structural and functional alterations of the gut barrier after injury by stimulating the epithelial cell metabolism and turnover; improving the intestinal blood flow; and increasing the systemic and local immune response, the secretion of IgA, and the production of trophic hormones (13–18).

In intensive care unit or liver transplant patients, some authors reported better outcome in patients receiving EEN compared with TPN (19–23), whereas no significant difference was observed in other trials (24–27). These contrasting results might be caused by the small number of patients studied and differences in the nutritional protocols.

In surgical patients, several authors have reported nutritional and metabolic

Table 6. Outcome in all the patients

	Parenteral (n = 131)	Enteral (n = 126)
Patients with infectious complications (%)	30 (22.9)	25 (19.8)
Patients with noninfectious complications (%)	23 (17.5)	20 (15.8)
Overall patients with any complication (%)	53 (40.4)	45 (35.6)
Patients with major complications (%)	21 (16)	16 (12.6)
Repeat operation	10 (7.6)	8 (6.3)
ICU transfer	5 (3.8)	4 (3.1)
Interventional radiology	6 (4.5)	4 (3.1)
Death (%)	4 (3.0)	3 (2.3)
Sepsis score (mean ± SD)	10.4 ± 3.7	8.5 ± 3.5
Length of hospital stay (days) (mean ± SD)	20.7 ± 8.8	19.9 ± 8.2

ICU, intensive care unit.

Table 7. Detail of complications

	Parenteral (n = 131)	Enteral (n = 126)
Infectious complications	36	27
Abdominal abscess	11	9
Wound infections	8	6
Infected pancreatic or biliary fistula	5	4
Pneumonia	6	3
Urinary tract infection	4	4
Sepsis	2	1
Noninfectious complications	38	35
Anastomotic leak (GI, pancreatic, biliary)	11	9
Delayed gastric emptying	9	7
Sterile pancreatic fistula	8	7
Hemoperitoneum	4	5
Gastrointestinal bleeding	3	3
Respiratory failure	2	2
Cardiac failure	1	2
Overall	74	62

GI, gastrointestinal.

Table 8. Outcome in the subgroup of malnourished patients (n = 91)

	Parenteral (n = 48)	Enteral (n = 43)
Patients with infectious complications (%)	12 (25.0)	6 (13.9)
Patients with noninfectious complications (%)	13 (27.0)	10 (23.2)
Overall patients with any complication (%)	25 (52.0)	16 (37.1)
Patients with major complications (%)	12 (25.0)	9 (20.9)
Repeat operation	5 (10.4)	4 (9.3)
ICU transfer	3 (6.2)	3 (6.9)
Interventional radiology	4 (8.3)	2 (4.6)
Death (%)	2 (4.1)	1 (2.3)
Sepsis score (mean ± SD)	11.3 ± 3.3	9.2 ± 3.6
Length of hospital stay (days) (mean ± SD)	22.6 ± 9.7	19.8 ± 8.9 ^a

ICU, intensive care unit.

^a*p* = .042 vs. total parenteral nutrition.

advantages of intestinal infusion of nutrients early after the operation (28–31). However, only a few small trials addressed the effect of enteral feeding on postoperative morbidity and outcome after major abdominal surgery, and the po-

tential advantages of EEN over TPN have never been substantiated by definitive data. In 1996, Carr et al. (6) published a prospective randomized study carried out in 28 patients. They found better nitrogen balance and better gut barrier func-

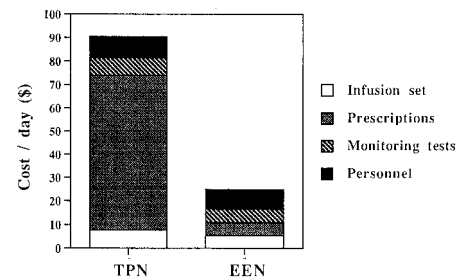


Figure 2. Cost analysis of the two nutritional regimens. TPN, total parenteral nutrition; EEN, early enteral nutrition.

tion in the group treated with EEN compared with the patients receiving conventional feeding protocol (fluids and electrolytes, oral food on POD 6). In 1997, Sand et al. (7) randomized 28 patients undergoing total gastrectomy, and they did not find significant differences in postoperative infections and length of postoperative stay between EEN and TPN. However, TPN was four-fold more expensive than EEN. In 1997, Watters (32) reported that, in a series of 13 patients, immediate postoperative enteral feeding resulted in impaired respiratory function. Indeed, the feeding protocol was very aggressive (caloric goal, 2500 kcal/day; to be reached on the second postoperative morning), and the rate of abdominal distension was 60%, which is considerably higher than other published experiences. The impaired respiratory mechanics might have been the result of abdominal discomfort related to the aggressive enteral infusion. In 1997, Heslin (33) reported that EEN enriched with specific substrates did not decrease morbidity compared with solely fluid replacement. However, the caloric intake by enteral feeding was about 30% of the goal in the first 10 days after surgery. Thus, the lack of benefit of enteral feeding might be partially attributed to the limited nutrient intake.

In the present trial, EEN was safe and well tolerated according to previous experiences (8, 11, 34). Moreover, the rate of both glucose metabolism alterations and electrolyte abnormalities were lower during EEN than during TPN. Despite the fact that the frequency of postoperative discomfort associated with EEN was 43%, achievement of the full nutritional goal was observed in 80% of the cases.

The evaluation of the postoperative immune response did not show any difference between EEN and TPN. In all patients, nutritional and immune vari-

The feasibility and safety, the low prevalence of metabolic adverse effects, the improved gut oxygenation, and the low cost of enteral feeding recommend its use in upper gastrointestinal tract cancer patients requiring postoperative artificial nutrition.

ables were significantly reduced immediately after surgery, and this alteration persisted until POD 8, regardless of the route of nutrient administration. Similarly, no difference was found in the postoperative inflammatory response.

We observed that surgical trauma was associated with a lowering of oxygen tension in both groups, which may represent a physiologic postoperative response. This response could be prolonged by leaving the gut at rest by using TPN. In contrast, the patients who received EEN had a significant faster recovery of oxygen tension from POD 5, suggesting that full enteral regimen may be needed to enhance intestinal blood supply. These are the first *in vivo* clinical data showing an effect of enteral nutrition on local oxygen tension. Nevertheless, these results were partially unexpected because animal data repeatedly suggested that small enteral volume is enough to improve significantly the intestinal blood flow and to ameliorate the gut barrier function and morphology after injury-induced damage (16–18, 35). The augmentation of intestinal function and blood flow has been hypothesized to be linked to the ability of luminal foodstuff to stimulate the local sympathetic and parasympathic neural pathways, and to release trophic and vasoactive hormones, cytokines, mediators, and prostanoids; and to a direct effect of nutrients on blood vessels (16–18, 35). It is difficult to translate experimental results into the clinical setting, but it is possible that, in humans, the effect of minimal jejunal feeding on gut is not

associated with a perceptible increase of oxygen tension, as shown by the polarographic probes. Our results suggest instead that a remarkable effect on gut oxygenation is obtained only when intraluminal stimulation of nutrients is maximal by high enteral volume or after some days of infusion.

In our series, outcome was comparable in the two groups. The lack of the expected clinical benefit of EEN in the overall population might be attributed to several factors: in well-nourished elective surgical patients, artificial nutrition by any route is an auxiliary therapy, and, thus, the clinical impact of nutrition may be limited and a substantial effect on outcome difficult to obtain. Moreover, in this type of patient, the potential loss of gut barrier function and the subsequent protective effect of enteral feeding are doubtful. The scenario may be quite different in malnourished patients, who have preoperative deficit of macronutrients and trace elements; thus, a complete nutritional support becomes an essential part of perioperative surgical care (36, 37). Moreover, malnutrition is a well-known risk factor for depressed systemic and intestinal immune response, impaired digestive, absorptive and barrier function, altered morphology and architecture, and reduced turnover of the epithelial layer (16–18). In this situation, microbial translocation to systemic organs may become massive and clinically relevant when gut barrier failure is coupled with mesenteric hypoperfusion or bacterial overgrowth (38–40). Thus, the presence of nutrients in the gut lumen may be an important stimulus for intestinal proper function and the protective effect of enteral nutrition might be responsible for the improved outcome compared with TPN (19–22). Our data support the above hypothesis. In fact, we observed that early gut feeding was more beneficial in the subgroup of malnourished patients possibly because of the more physiologic administration and utilization of nutrients. The lack of significant difference between EEN and TPN in the subgroup of malnourished subjects for morbidity rate may be caused partially by a type II error.

In 1991, the Department of Veterans Affairs multicenter trial (36) showed that TPN administered perioperatively to surgical patients was detrimental with a significant increase of infectious morbidity. In contrast, a *post hoc* analysis, performed in a subgroup of severely malnourished patients (n = 50 overall), TPN

was able to reduce the rate of noninfectious complications. In this study, a group receiving enteral feeding was not included so that the potential advantages of the enteral route could not be addressed. A subsequent European multicenter trial (37) confirmed the above data in malnourished patients and suggested that perioperative enteral feeding was of no further benefit when compared with TPN. Nevertheless, it was difficult to draw any definitive conclusion because the number of malnourished patients was small (18 in the TPN group and 13 in the enteral group). In this context, our data are original for the relative large sample size of malnourished patients (91 overall) and, for the first time, suggest that, in depleted cancer patients undergoing major upper GI tract surgery, the early infusion of nutrients in the gut lumen may reduce postoperative infectious morbidity compared with TPN.

According to other studies (7, 27, 41), EEN was considerably less expensive than TPN. By using EEN instead of TPN, the daily saving was \$65, and the mean saving for the entire duration of nutritional support (13 days) was \$845 per patient. In our analysis, the difference was made essentially by the cost of the nutritional formulas, with other variables such as sanitary personnel, diagnostic procedures or infusion devices being similar between the two groups. In addition, the costs of complications and length of stay, even although not calculated in the present trial, might be in favor of the EEN group, particularly considering depleted patients.

In conclusion, in the present trial, early enteral nutrition did not improve outcome compared with parenteral nutrition in the overall population. However, by considering a subgroup of malnourished patients, the administration of nutrients through the enteral route, compared with the parenteral one, was associated with a significant shorter length of stay. This may be a result of the lower rate of complications. The feasibility and safety, the low prevalence of metabolic adverse effects, the improved gut oxygenation, and the low cost of enteral feeding recommend its use in upper GI tract cancer patients requiring postoperative artificial nutrition.

REFERENCES

1. ASPEN Board of Directors: Guidelines for the use of parenteral and enteral nutrition in

- adult and pediatric patients. *J Parenter Enter Nutr* 1993; 17(suppl): 5–11
2. French Speaking Society for Parenteral and Enteral Nutrition: Perioperative artificial nutrition in elective adult surgery. *Clin Nutr* 1996; 15:223–229
 3. Italian Society for Parenteral and Enteral Nutrition: Linee guida per l'impiego della nutrizione parenterale ed enterale nei pazienti adulti ospedalizzati. *Riv Ital Nutr Parenter Enter* 1995; 13(suppl):43–45
 4. Jolliet P, Pichard C, Biolo G, et al: Enteral nutrition in intensive care patients: A practical approach. *Int Care Med* 1998; 24: 848–859
 5. Klein S, Kinney J, Jeejeebhoy K, et al: Nutritional support in clinical practice: Review of published data and recommendation for future research directions. *J Parenter Enter Nutr* 1997; 21:133–156
 6. Carr CS, Ling E, Boulos P, Singer M: Randomised trial of safety and efficacy of immediate postoperative enteral feeding in patients undergoing gastrointestinal resection. *Br Med J* 1996; 312:869–871
 7. Sand J, Luostarinen M, Matikainen M: Enteral or parenteral feeding after total gastrectomy: Prospective randomized pilot study. *Eur J Surg* 1997; 163:761–766
 8. Braga M, Gianotti L, Vignali A, et al: Artificial nutrition after major abdominal surgery: Impact of route of administration and composition of the diet. *Crit Care Med* 1998; 26: 24–30
 9. Kavet RJ, Brain JD: Methods to quantify endocytosis. *J Reticuloendothelial Soc* 1980; 27:201–221
 10. Jacobi CA, Zieren HU, Mullen JM, et al: Anatomic tissue oxygen tension during esophagectomy in patients with esophagus carcinoma. *Eur Surg Res* 1996; 28:26–31
 11. 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 neoplasms. *Arch Surg* 1997; 132:1222–1230
 12. Elebute EA, Stoner HB: The grading of sepsis. *Br J Surg* 1983; 70:29–31
 13. Lin M-T, Saito H, Fukushima R, et al: Route of nutritional supply influences local, systemic, and remote organ responses to intraperitoneal bacterial challenge. *Ann Surg* 1996; 223:84–93
 14. Gianotti L, Alexander JW, Nelson JL, et al: Role of early enteral feeding and acute starvation on postburn bacterial translocation and host defense: Prospective randomized trial. *Crit Care Med* 1994; 22:265–272
 15. Gianotti L, Nelson JW, Alexander JW, et al: Postinjury hypermetabolic response and magnitude of bacterial translocation: Prevention by early enteral nutrition. *Nutrition* 1994; 10:225–231
 16. Lara TM, Jacob DO: Effect of critical illness and nutritional support on mucosal mass and function. *Clin Nutr* 1998; 17:99–105
 17. Spitz J, Gandhi S, Hecht G, Alverdy J: The effect of total parenteral nutrition on gastrointestinal function. *Clin Nutr* 1993; 12(Suppl 1):S33–S37
 18. Johnson CD, Kudsk KA: Nutrition and intestinal mucosal immunity. *Clin Nutr* 1999; 18: 337–344
 19. Kudsk KA, Croce MA, Fabian TC, et al: Enteral versus parenteral feeding. *Ann Surg* 1992; 215:503–513
 20. Moore FA, Feliciano DV, Andrassy RJ, et al: Total enteral feeding compared with parenteral reduces postoperative septic complications: The results of a meta-analysis. *Ann Surg* 1992; 216:172–183
 21. Hasse JM, Blue LS, Liepa G, et al: Early enteral nutrition support in patients undergoing liver transplant. *J Parenter Enter Nutr* 1995; 19:437–443
 22. Chiarelli A, Enzi G, Casadei A, et al: Very early nutritional supplementation in burned patients. *Am J Clin Nutr* 1990; 51:1035–1039
 23. Hadfield RJ, Sinclair DG, Houldsworth PE, et al: Effects of enteral and parenteral nutrition on gut mucosal permeability in the critically ill. *Am J Respir Crit Care Med* 1995; 152: 1545–1548
 24. Adams S, Dellinger PE, Wertz MJ, et al: Enteral versus parenteral nutritional support following laparotomy for trauma: A randomized prospective trial. *J Trauma* 1986; 26: 882–891
 25. Dunham CM, Frankenfield D, Belzberg H, et al: Gut failure: Predictor of or contributor to mortality in mechanically ventilated blunt trauma patients? *J Trauma* 1994; 37:30–34
 26. Cerra FB, McPherson JP, Konstantinides FN, et al: Enteral nutrition does not prevent multiple organ failure (MOFS) after sepsis. *Surgery* 1988; 104:727–733
 27. Wicks C, Somasundaram S, Bjarnason I, et al: Comparison of enteral feeding and total parenteral nutrition after liver transplantation. *Lancet* 1994; 344:837–840
 28. Harrison LE, Hochwald, Heslin MJ, et al: Early postoperative enteral nutrition improves peripheral protein kinetics in upper gastrointestinal cancer patients undergoing complete resection: A randomized trial. *J Parenter Enter Nutr* 1997; 21:202–207
 29. Bower RH, Talamini M, Sax HC, et al: Postoperative enteral vs. parenteral nutrition. *Arch Surg* 1986; 121:1040–1045
 30. Hoover HC, Ryan JA, Anderson EJ, et al: Nutritional benefits of immediate postoperative jejunal feeding of an elemental diet. *Am J Surg* 1980; 139:153–159
 31. Fong Y, Marano MA, Barber A, et al: Total parenteral nutrition and bowel rest modify the metabolic response to endotoxin in humans. *Ann Surg* 1989; 210:449–456
 32. Watters JM, Kirkpatrick SM, Norris SB, et al: Immediate postoperative enteral feeding results in impaired respiratory mechanics and decreased mobility. *Ann Surg* 1997; 226: 369–380
 33. 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
 34. Braga M, Gianotti L, Cestari A, et al: Gut function, immune and inflammatory responses in patients perioperatively fed with supplemented formulas. *Arch Surg* 1996; 131:1257–1265
 35. Inoue S, Luke S, Alexander JW, et al: Increased gut blood flow with early enteral feeding in burned guinea pigs. *J Burn Care Rehabil* 1989; 10:300–308
 36. The Veteran Affairs Total Parenteral Nutrition Cooperative Study Group: Perioperative total parenteral nutrition in surgical patients. *N Engl J Med* 1991; 325:525–532
 37. Von Meyenfeld M, Meijerink W, Rouffart M, et al: Perioperative nutritional support: a randomized clinical trial. *Clin Nutr* 1992; 11:180–186
 38. Gianotti L, Alexander JW, Fukushima R, et al: Translocation of *Candida albicans* is related to the blood flow of individual intestinal villi. *Circ Shock* 1993; 40:250–257
 39. Redan JA, Rush BF, McCullough JN, et al: Organ distribution of radiolabeled enteric *E. coli* during and after hemorrhagic shock. *Ann Surg* 1990; 211:663–668
 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
 41. Salis C, Paccagnella A, Vannucci A, et al: Studio multicentrico italiano per la valutazione delle risorse utilizzate nella nutrizione artificiale (VURNA) in pazienti ospedalizzati. *Riv Ital Nutr Parenter Enter* 1998; 16:14–24