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PERIOPERATIVE TOTAL PARENTERAL NUTRITION IN SURGICAL PATIENTS

THE VETERANS AFFAIRS TOTAL PARENTERAL NUTRITION COOPERATIVE STUDY GROUP*

Abstract *Background.* We undertook this study to test the hypothesis that perioperative total parenteral nutrition (TPN) decreases the incidence of serious complications after major abdominal or thoracic surgical procedures in malnourished patients.

Methods. We studied 395 malnourished patients (99 percent of them male) who required laparotomy or noncardiac thoracotomy. They were randomly assigned to receive either TPN for 7 to 15 days before surgery and 3 days afterward (the TPN group) or no perioperative TPN (the control group). The patients were monitored for complications for 90 days after surgery.

Results. The rates of major complications during the first 30 days after surgery in the two groups were similar (TPN group, 25.5 percent; control group, 24.6 percent), as were the overall 90-day mortality rates (13.4 percent and 10.5 percent, respectively). There were more infectious complications in the TPN group than in the controls (14.1 vs. 6.4 percent; P = 0.01; relative risk, 2.20; 95 percent confidence interval, 1.19 to 4.05), but slightly more noninfectious complications in the control group (16.7 vs. 22.2 percent; P = 0.20; relative risk, 0.75; 95 percent confidence interval, 0.50 to 1.13). The increased rate of infections was confined to patients categorized as either borderline or mildly malnourished, according to Subjective Global Assessment or an objective nutritional assessment, and these patients had no demonstrable benefit from TPN. In contrast, severely malnourished patients who received TPN had fewer noninfectious complications than controls (5 vs. 43 percent; P = 0.03; relative risk, 0.12; 95 percent confidence interval, 0.02 to 0.91), with no concomitant increase in infectious complications.

Conclusions. The use of preoperative TPN should be limited to patients who are severely malnourished unless there are other specific indications. (N Engl J Med 1991; 325:525-32.)

MALNOURISHED surgical patients are at greater risk for postoperative morbidity and mortality than well-nourished patients undergoing similar operations for similar indications.[1] Studies attempting to define the effect of preoperative nutritional support, usually total parenteral nutrition (TPN), on the incidence of postoperative complications have been inconclusive,[2,3] making it uncertain whether the benefits of preoperative TPN are sufficient to justify its use in malnourished surgical patients who are otherwise candidates for elective surgery. We describe the results of a cooperative multi-institutional clinical trial conducted by the Department of Veterans Affairs (VA) and designed to assess the efficacy of perioperative TPN in malnourished patients undergoing major intrathoracic or intraperitoneal operations. Our primary study objective was to determine whether perioperative TPN reduces major operative complications, mortality, or both in such patients.

METHODS

The complete protocol of the clinical trial has been published elsewhere[3,4] but is summarized here. The study was approved by the VA Cooperative Studies Human Rights Committee and local institutional review boards at the participating centers. Informed consent was obtained from the study subjects before their entry into the study.

Selection of Patients

All patients at least 21 years old who were admitted to a participating VA Medical Center before nonemergency laparotomy or thoracotomy were potentially eligible for the study. Laparotomy was defined as any nonvascular intraperitoneal operation, excluding inguinal or ventral herniorrhaphy, and thoracotomy as any noncardiac intrathoracic operation, excluding mediastinoscopy or mediastinotomy. Patients were excluded from the study if they were expected to die of their primary disease within 90 days, had received TPN in the preceding 15 days, or had undergone an operation in the preceding 30 days. The remaining patients were considered potentially eligible for the study and were screened for any condition or conditions that would make participation impossible or potentially dangerous or that could have a substantial effect on the operative outcome that was independent of nutritional status. These reasons for exclusion are listed in Table 1; the criteria for their diagnosis have been described elsewhere.[1]

The patients not excluded for these reasons then underwent nutritional screening. They were considered malnourished if they met

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Table 1. Reasons for the Exclusion of Patients from the Study.

Patient Category or Reason for Exclusion	No. of Patients
Potentially eligible patients	3259
Patients with specific reason for exclusion	811*
Delay in surgery contraindicated	253
TPN contraindicated	23
Type IV hyperlipidemia	8
Fluid restriction (<1000 ml/24 hr)	6
Central venous access contraindicated	9
Major concurrent illness	488†
Cardiac	74
Neurologic	151
Hepatic	154
Pulmonary	27
Renal	53
Coagulopathy	46
Psychiatric	318
TPN essential	97
Pancreatitis or pseudocyst	19
Partial bowel or gastric-outlet obstruction	54
Other gastrointestinal disease	24
Patients remaining after exclusions	2448
Patients who did not meet nutritional criteria (well-nourished nonrandomized group)	1497
Patients remaining after nutritional screening	951
Patients discharged without surgery	169
Patients eligible for randomization	782
Patients who declined randomization (malnourished nonrandomized group)	323
Patients entering the study	459

*The total of the specific exclusions shown below exceeds this number because some patients met more than one criterion for exclusion.

†The total number of cases of the concurrent diseases listed exceeds this number because some patients had more than one disease.

either or both of two criteria: (1) a score of 100 or less on the Nutrition Risk Index, calculated according to the following formula:

$$1.519 \times \text{the serum albumin level (in grams per liter)} + 0.417 \times (\text{current weight/usual weight}) \times 100$$

or (2) any two of the following: a current weight that was 95 percent of the ideal weight or less; a serum albumin level of 39.2 g per liter or less; or a serum prealbumin level of 186 mg per liter or less.

The methods used to develop these criteria have been described elsewhere.[3] Patients who were too well nourished to meet either criterion were not offered study participation but were assigned to the well-nourished nonrandomized group and followed to monitor postoperative complications. The malnourished patients were informed about the study according to the VA guidelines and asked to participate. Those who declined to do so were assigned to the malnourished nonrandomized group and followed to monitor postoperative complications.

Randomized Groups and Monitoring of Complications

The patients who entered the study were randomly assigned by computer-generated random numbers to the TPN group or the control group. Patients with cancer and those without it were randomized separately to ensure an equal distribution between groups. Patients who initially consented to participate in the study but later withdrew underwent no further protocol-driven nutritional interventions or testing but were followed to monitor postoperative complications; these patients were included in the final analyses.

The patients in the TPN group received perioperative TPN through a central venous catheter in doses increasing for 72 hours to a daily caloric goal of 1000 kcal above the resting metabolic expenditure, as defined elsewhere.[4] Five hundred fifty kilocalories were provided as lipid (Intralipid, KabiVitrum Laboratories, Alameda, Calif.), and the remainder as dextrose. Crystalline amino acids (Freamine III, Kendall McGaw Laboratories, Irvine, Calif.) were provided at a calorie:nitrogen ratio of 150 kcal:1 g of nitrogen. Vitamins (MVI-12 [10 ml], Armour Pharmaceutical, West Chester, Pa.) and trace elements (trace-element mix [1.0 ml], Armour) were provided daily, and electrolytes were provided as clinically indicated.

The daily TPN intake was considered adequate if the intake of macronutrients was ≥85 percent of the calculated goal. Optimal TPN was defined as 7 to 15 days of preoperative treatment at adequate levels. Patients who did not receive optimal TPN were included in the final analyses but were identified as suboptimally treated. The patients receiving TPN were permitted to eat as clinically indicated; their oral intake was recorded but not included in the determination of the adequacy of the daily intake of macronutrients. Postoperatively, TPN was continued for 72 hours; thereafter it could be continued or terminated as clinically indicated.

The control patients received no TPN (or forced enteral feedings) before surgery or for the first 72 hours after surgery. Thereafter, TPN or tube feedings could be instituted if clinically indicated. The control patients were given an oral diet as clinically indicated. Their food intake was monitored by the study dietitian, but the calorie counts were not charted except at the request of the patient's physician.

The patients receiving TPN underwent surgery after receiving adequate TPN for at least seven days. The control patients underwent surgery after at least three days of base-line observation. Surgery was permitted earlier in either group if clinically indicated.

The patients were monitored for complications related to either the operation or TPN therapy from the day of randomization until death or postoperative day 90. Complications were classified as major or minor and also as infectious or noninfectious. Monitoring included direct observation of the patient and chart review daily, continuing after discharge with biweekly clinic visits, telephone interviews, or both. The monitoring methods, objective criteria used to diagnose complications, and protocols for the evaluation of fever and suspected bacteremia have been described elsewhere.[4]

Statistical Approach

The primary end point for comparison was the incidence of major operative complications. On the basis of previous studies,[3] we anticipated a 20 percent rate of major complications after 30 days in the control group. A reduction of this rate by half (to 10 percent) in the TPN group would be considered clinically important. Detecting a difference of this magnitude or greater at a level of statistical significance of 0.05 and a power of 0.90, with a one-tailed test of proportions, would require that there be 255 patients in each group. Thus, the goal for the accrual of patients was 510 patients for the final outcome analysis.

Five additional subanalyses to be tested by two-tailed tests were defined a priori as secondary end points. These were the comparisons of the TPN and control groups with respect to mortality, all complications (major or minor), infectious complications, noninfectious complications, and major complications after stratification according to the severity of the patient's underlying malnutrition. Nutritional status was stratified according to the Nutrition Risk Index and the Subjective Global Assessment, as described by Baker et al.[5] When the Nutrition Risk Index score was used, the patients were categorized as borderline malnourished (Nutrition Risk Index score, >97.5), mildly malnourished (83.5 to 97.5), or severely malnourished (<83.5). Various combinations of weight loss and hypoalbuminemia result in Nutrition Risk Index values below 83.5. In the absence of weight loss (when the patient's current weight divided by the usual weight equaled 1.0), serum albumin levels below 27.8 g per liter were required for a patient to be considered severely malnourished. With marked weight loss (e.g., current weight/usual weight = 0.8), only mild hypoalbuminemia (<33.1 g per liter) is required for the Nutrition Risk Index values to fall below 83.5. Stratification with the Subjective Global Assessment was performed on the basis of clinical information obtained from a thorough history and physical examination without knowledge of specific laboratory or anthropometric measures. The examiner came to a global

assessment of the patient's nutritional status on the basis of the presence or absence of historical features or physical stigmata associated with malnutrition, without reference to a rigid scoring system based on specific criteria. At the time of the screening to determine eligibility for the study, each patient was assigned a Subjective Global Assessment rating of borderline malnourished (no stigmata of malnutrition despite having satisfied study entry criteria; corresponds to "well-nourished" rating by Baker et al.[5]), mildly malnourished (few or mild stigmata), or severely malnourished (multiple or severe stigmata or both).

Data were submitted to the Perry Point VA Cooperative Studies Program (CSP) Coordinating Center within 30 days, and interim analyses of outcome measures were performed every 9 months. The interim results were not revealed to the participating investigators but were reviewed by the CSP Human Rights Committee and the Study Operations Committee to ensure the safety of patients and to determine whether the study should be terminated prematurely.

Continuous variables were compared by analysis of variance, and categorical variables by either the chi-square test or Fisher's exact test. Analyses of categorical covariates were performed by the Mantel–Haenszel technique. All statistical analyses were two-tailed and were based on the intention-to-treat concept.

Results

Randomized Groups and Comparisons at Base Line

During the 26 months of patient accrual, 3259 patients were identified as potentially eligible for the study. Of these, 811 patients (25 percent) were excluded for one or more of the reasons shown in Table 1. Two hundred fifty-three patients were excluded because a delay in surgery of 7 to 10 days was contraindicated, 23 because TPN could not be administered or was potentially dangerous, 488 because concurrent illnesses or a psychiatric disorder precluded informed consent, and 97 (3 percent) because TPN was considered essential. Most of these 97 patients required preoperative TPN to permit bowel rest or decompression for at least three to five days before laparotomy.

Of the remaining 2448 patients who underwent nutritional screening, 1497 (61 percent) did not meet either of the nutritional criteria and were assigned to the well-nourished nonrandomized group. Of these patients, 1220 underwent surgery, and follow-up data were available for 1218. Nine hundred fifty-one patients met one or both nutritional criteria, but additional clinical evaluation before randomization showed that surgery was not indicated in 169, and they were discharged. The remaining 782 patients were eligible for randomization and were asked to participate in the study. Of these patients, 323 (41 percent) were not randomized because of refusal by the patient's physician (56 patients) or the patient (233) or for unstated reasons (34). These 323 patients were assigned to the malnourished nonrandomized group; 305 of them underwent surgery, and follow-up data were available for all 305.

During the 26-month period initially allocated to and funded for the accrual of patients, 459 patients (455 men and 4 women) consented to participate in the study and were randomly assigned to the TPN group (231) or the control group (228). Of these, 395 (86 percent) underwent surgery. Although the size of this sample fell short of the original projections, the interim analysis indicated that extending the recruitment period would be unlikely to alter the results of the study, and therefore the enrollment of patients was terminated. The sample accrued (395 patients) was not sufficient to test the original one-tailed hypothesis (that the 30-day rate of major complications would be reduced from 20 percent to 10 percent with TPN) with a power of 0.90, but it did provide a power of 0.80. Since the actual rate of major complications in the control group was approximately 25 percent, the 395 patients studied did provide a power of 0.89 for testing a revised hypothesis involving a 25 percent rate of major complications in the control group as compared with 12.5 percent in the TPN group.

The characteristics of the study patients relative to those of the patients in the two nonrandomized groups are shown in Table 2. The study group was older and more malnourished and included more patients with gastrointestinal cancer than the well-nourished nonrandomized group. In most respects, the study group was similar to the malnourished nonrandomized group, although the study group was slightly more malnourished according to some criteria and included more patients with gastrointestinal cancer. The postoperative rates of morbidity and mortality were higher after 30 days in the study group than in the well-nourished nonrandomized group but were similar to those in the malnourished nonrandomized group.

The TPN group and the control group were similar ($P>0.15$) with respect to age, sex, race, diagnosis, and

Table 2. Base-Line Characteristics and Outcomes 30 Days after Surgery in the Study Group and the Nonrandomized Groups.*

Variable	Study Group	Nonrandomized Groups	
		Well-nourished	Malnourished
No. of patients	459	1218†	305†
Age (yr)	62.9±9.9	59.6±10.6	62.3±10.6
Diagnosis (%)			
GI cancer	51	28	32
Lung cancer	11	13	15
Other cancer	4	4	2
Benign GI disease	27	45	38
Other benign disease	7	10	13
Nutritional status			
Body weight (kg)	66±13.6	79±15.5	70±14.0
% Usual weight	89±8.0	97±5.6	92±7.9
Serum albumin (g/liter)	37±3.6	43±2.7	37±3.8
Serum prealbumin (mg/liter)	164±77.7	254±66.6	174±79.3
Triceps skin-fold (mm)	11±6.1	16±8.2	13±7.1
Borderline malnourished by SGA (%)	30	89	45
Outcome (%)			
Mortality	6.0	2.3	4.9
Complications	37	21	31

*Plus–minus values are means ±SD. GI denotes gastrointestinal, and SGA Subjective Global Assessment.

†Numbers of patients shown for the nonrandomized groups include all patients who underwent surgery and for whom follow-up data were available.

most measures of nutritional status (serum prealbumin level, weight, percentage of ideal weight, triceps skin-fold thickness, arm-muscle circumference, and grip strength). Table 3 shows the diagnoses and nutritional measures in which the two study groups had differences approaching or reaching statistical significance. When such differences occurred, the base-line nutritional depletion was uniformly more severe in the TPN group. However, a Mantel–Haenszel categorical covariate analysis of outcome measures, with control for the presence or absence of cancer, Subjective Global Assessment classification, and Nutrition Risk Index, did not alter the relative risks reported here (Table 4) — indicating that these imbalances did not alter the substantial findings of the study.

Four patients died before surgery (2 in each group), and 60 patients (37 in the TPN group and 23 in the control group) were discharged without an operation when additional studies revealed surgery to be inappropriate or when the patient refused the operation. Table 5 shows the operative procedures undergone by the remaining 192 patients receiving TPN and 203 control patients.

Nutrient Intake and Treatment-Related Complications

Of the 192 patients receiving TPN who underwent surgery, 130 completed an optimal course of TPN, 49 received suboptimal TPN, and 13 received no TPN after an initial attempt to place a central line failed and the patient refused further attempts. The mean duration of preoperative TPN at adequate levels was 7.9 days (range, 0 to 16). The intravenous, oral, and total mean preoperative daily caloric intakes for patients receiving TPN were 2109 kcal (range, 331 to 2883), 834 kcal (range, 0 to 2110), and 2944 kcal (range, 420 to 4543), respectively. Of the 203 control patients who underwent surgery, 3 who could not eat were given preoperative TPN when clinical conditions required that surgery be delayed by five or more days. The remaining control patients received no preoperative TPN or forced enteral feedings. The mean preoperative daily intake of calories by mouth in this group was 1280 kcal (range, 0 to 3342). Postoperatively, 111 patients in the TPN group received TPN for more than the three days required by the protocol, and TPN was instituted after postoperative day 3 in 24 control patients.

One hundred seventy-nine patients in the TPN group underwent a total of 310 insertions or changes of a central venous catheter, whereas 84 control patients underwent a total of 93 catheter insertions or changes for indications other than TPN. Catheter-

Table 3. Base-Line Characteristics of the Randomized Patients.*

Characteristic	TPN Group (N = 192)	Control Group (N = 203)	P Value
Serum albumin (g/liter)	36.5±3.6	37.1±3.7	0.06
% Usual body weight	88.9±7.6	90.4±8.0	0.12
Nutrition Risk Index score	92.3±6.4	93.8±6.0	0.01
Subjective Global Assessment (%)			
Borderline malnourished	22	38	
Mildly malnourished	62	53	
Severely malnourished	15	9	0.03
	no. of patients		
Cancer			
Esophageal or gastric	41	34	
Pancreatic or hepatobiliary	13	13	
Colorectal	42	57	
Lung	19	24	
Other	10	10	
All types	125 (65%)	138 (68%)	
Other diseases			
Esophageal or gastric	11	12	
Pancreatic or biliary	25	26	
Small or large bowel	11	9	
Lung or mediastinal	6	5	
Other benign disorders	14	13	
All types	67 (35%)	65 (32%)	

*Plus–minus values are means ±SD.

Table 4. Complications Observed within 30 Days of Surgery.*

Type of Complication	TPN Group (N = 192)	Control Group (N = 203)
	no. of episodes/no. of patients	
Major, infectious		
Pneumonia or empyema	17/16	9/9
Abdominal abscess	2/2	2/2
Extra-abdominal abscess	1/1	0
Fasciitis	3/3	0
Bacteremia or fungemia	8/7	5/5
Other septic complications	,0	1/1
Total	31/27	17/13
Patients affected (%)	14.1	6.4
Relative risk (TPN:control) = 2.20		
95% Confidence interval, 1.19–4.05		
Relative risk with control for SGA = 2.23		
Major, noninfectious		
Anastomotic leak	7/6	12/11
Bronchopleurocutaneous fistula	4/3	6/6
Wound dehiscence	1/1	1/1
Decubitus ulcer	1/1	1/1
Chronic respiratory failure (≥4 days)	14/13	12/11
Gastrointestinal complications†	11/10	17/14
Cardiovascular complications‡	15/15	18/15
Pulmonary embolus	0	1/1
Renal failure	0	3/3
Total	53/32	71/45
Patients affected (%)	16.7	22.2
Relative risk (TPN:control) = 0.75		
95% Confidence interval, 0.50–1.13		
Relative risk with control for SGA = 0.71		
Minor, infectious		
Wound infection	14/12	5/4
Urinary tract infection	17/13	19/14
Minor, noninfectious		
Uncomplicated arrhythmia	14/11	22/20
Atelectasis	6/6	13/8
Transient respiratory failure§	6/6	6/6
Catheter-related		
Pneumothorax	4/4	0
Mediastinal hematoma	1/1	0
Hydrothorax	2/2	0
Air or catheter embolus	3/3	1/1
Thrombosis	1/1	1/1

*The total numbers of patients shown for major complications are less than the sum of the patients listed as having individual complications because many patients had more than one complication. SGA denotes Subjective Global Assessment.

†Includes bleeding, obstruction, perforation, and ischemia.

‡Includes myocardial infarction, cardiogenic shock, cardiac arrest, and stroke.

§Respiratory failure requiring the use of a ventilator for ≤3 days postoperatively.

Table 5. Operative Procedures Performed in the Randomized Patients.

Type of Procedure	TPN Group	Control Group	Both
Thoracotomy			
Pneumonectomy	2	7	9
Lobectomy	10	14	24
Wedge resection	6	4	10
Other	5	4	9
Laparotomy*			
Esophagectomy or esophagogastrectomy	21	21	42
Other esophageal procedures	4	3	7
Gastrectomy or gastric drainage	27	20	47
Small-bowel resection or bypass	6	5	11
Colon resection ± colostomy	57	68	125
Liver resection or biliary bypass	8	12	20
Cholecystectomy or cholecystostomy ± common duct exploration	14	18	32
Pancreatic resection or drainage	11	7	18
Urologic procedure	4	6	10
Laparotomy without GI resection or anastomosis†	17	14	31
All procedures	**192**	**203**	**395**

*Includes procedures combining laparotomy and thoracotomy.
†GI denotes gastrointestinal.

related complications were uncommon (Table 4), as were major metabolic disturbances, with only hyperglycemia (serum glucose level, >16.7 mmol per liter [300 mg per deciliter]) occurring in significantly more patients receiving TPN (38, as compared with 3 control patients). Bacteremia or fungemia occurred in seven patients receiving TPN and five control patients, with one episode attributable to a TPN catheter and the remainder to other causes.

Mortality and Complications

Thirty-one of the 231 patients initially assigned to the TPN group (13.4 percent) and 24 of the 228 patients assigned to the control group (10.5 percent) died during either the preoperative period or the 90-day postoperative period. As noted above, two patients in each group died before surgery, with one death in the TPN group possibly attributable to catheter sepsis. The 30-day postoperative mortality rates were 7.3 percent (14 of 192) and 4.9 percent (10 of 203) in the TPN and control groups, respectively. During the next 60 days, seven patients in the TPN group and nine in the control group died from complications of surgery. Thus, the 90-day rates of mortality related to complications were 10.9 percent and 9.4 percent in the TPN and control groups, respectively. An additional 11 patients (8 in the TPN group and 3 in the control group) died of disease progression or an unrelated process between postoperative days 30 and 90. None of these differences in mortality were statistically significant.

The rates of major complications during the first 30 postoperative days were similar in the two groups. Forty-nine of the 192 patients receiving TPN (25.5 percent) and 50 of the 203 control patients (24.6 percent) had such complications. The overall rates of complications (major or minor) after 30 days were 37.0 percent and 36.5 percent in the TPN and control groups, respectively. The rates of complications remained similar at 90 days, with major complications occurring in 28 percent of both groups. The patients in the TPN group who completed an optimal course of TPN had fewer major complications after 30 days than the patients with a suboptimal course (19.2 vs. 38.7 percent; $P<0.05$), but the rate in the patients completing an optimal course was not significantly lower than that in the control patients.

Although the overall rates of complications were similar, the types of complications in the two groups were different. The rates of individual complications and the relative risks and confidence intervals for the major categories of complications are shown in Table 4. One or more major infectious complications occurred in more patients receiving TPN than control patients during the first 30 postoperative days (14.1 vs. 6.4 percent; $P = 0.01$). One or more major noninfectious complications occurred slightly (but not significantly) more often in the control group than in the TPN group (22.2 vs. 16.7 percent; $P = 0.20$). These differences are not explained by differences in base-line nutritional status, as indicated by the similar relative-risk ratios with and without covariate analysis adjusting for base-line Subjective Global Assessment. Similarly, an analysis of rates of major complications according to medical center revealed no significant differences. This pattern persisted after 90 days, with more infectious complications in the patients receiving TPN (16.7, as compared with 9.4 percent for the controls; $P = 0.04$) and slightly more noninfectious complications in the controls (25.1, as compared with 19.3 percent for the patients receiving TPN; $P = 0.18$).

Complication rates after stratification according to base-line nutritional status are shown in Table 6. Among the control patients, the incidence of complications generally increased with increasing severity of malnutrition. This relation was not present in the patients receiving TPN, in whom the incidence of complications was similar in the various nutritional strata. The marked increase in infectious complications in the TPN group as a whole was confined to the patients identified as borderline malnourished (124 patients) or mildly malnourished (218 patients) by the Subjective Global Assessment or by a score ≥ 83.5 on the Nutrition Risk Index (362 patients). This difference reached statistical significance for the patients considered to be mildly malnourished on the basis of the Nutrition Risk Index (3.7 percent in the control group vs. 13.6 percent in the TPN group; $P = 0.004$) (Table 6). There were fewer noninfectious complications in the borderline malnourished and the mildly malnourished patients treated with TPN. Although these differences were not significant, they largely negated the increased incidence of infections, so that the overall rate of major complications (infectious plus noninfectious) was only minimally higher for the borderline malnourished patients who received TPN than for

Table 6. Cumulative Incidence of Complications 30 Days after Nutritional Stratification.

	Degree of Malnutrition*		
	BORDERLINE	MILD	SEVERE
Major infectious complications			
Subjective Global Assessment			
TPN group (%)	12.2	15.2	12.9
Control group (%)	4.0	6.6	10.5
P value (TPN vs. control)	0.15	0.05	1.00
Relative risk	3.05	2.30	1.23
95% Confidence interval	0.80–11.67	0.99–5.32	0.25–6.06
Nutrition Risk Index			
TPN group (%)	12.5	14.4	15.8
Control group (%)	9.1	3.7	21.4
P value	0.75	0.004	1.00
Relative risk	1.38	3.86	0.74
95% Confidence interval	0.45–4.22	1.48–10.08	0.17–3.12
Major noninfectious complications			
Subjective Global Assessment			
TPN group (%)	14.3	16.1	22.6
Control group (%)	16.0	22.6	42.1
P value	1.00	0.23	0.21
Relative risk	0.89	0.71	0.54
95% Confidence interval	0.38–2.11	0.41–1.23	0.23–1.24
Nutrition Risk Index			
TPN group (%)	12.5	20.0	5.3
Control group (%)	23.6	19.4	42.9
P value	0.20	1.00	0.03
Relative risk	0.53	1.03	0.12
95% Confidence interval	0.22–1.28	0.63–1.69	0.02–0.91

*Patients whose degree of malnutrition was evaluated as borderline had no stigmata of malnutrition on the Subjective Global Assessment or had scores above 97.5 on the Nutrition Risk Index. Mildly malnourished patients had few or mild stigmata on the Subjective Global Assessment or scores from 83.5 to 97.5 on the Nutrition Risk Index. Severely malnourished patients had multiple or severe stigmata, or both, on the Subjective Global Assessment or scores below 83.5 on the Nutrition Risk Index. See Methods for details.

controls (24.5 vs. 18.7 percent, P = 0.53), and it was nearly identical for the mildly malnourished patients in both groups (TPN, 25.9 percent; control, 24.5 percent).

Among the severely malnourished patients (a group numbering 50 on the basis of the Subjective Global Assessment and 33 on the basis of the Nutrition Risk Index), the frequency of infectious complications was similar in both the randomized groups. Noninfectious complications were less common in the severely malnourished patients receiving TPN, and this difference achieved statistical significance for patients with Nutrition Risk Index scores below 83.5 (42.9 vs. 5.3 percent for controls; P = 0.03) (Table 6). The overall rates of major complications were lower in the patients receiving TPN who were considered severely malnourished on the basis of the Subjective Global Assessment (25.8 vs. 47.4 percent; P = 0.12) or the Nutrition Risk Index score (21.1 vs. 46.7 percent; P = 0.11). These differences are numerically large but of marginal statistical significance, presumably because of the small size of the subgroups.

Discussion

We found no significant reduction in morbidity or mortality when TPN was provided to a heterogeneous group of surgical patients. The patients had no specific indications for preoperative TPN other than malnutrition, were candidates for either prompt or delayed surgery, were not preterminal, had not undergone surgery recently, and had no concurrent diseases causing major organ dysfunction. This is not to suggest that perioperative TPN would be inappropriate in patients with these characteristics, but we believed that the exclusion of such patients would reduce the confounding factors that might obscure any beneficial effect of TPN. The results of this trial will be most applicable to patients similar to those in the two randomized groups.

We also report outcome results for two nonrandomized populations. Although not directly relevant to the central findings, these results may be useful in assessing the validity of the results and their applicability to clinical settings outside the VA system. In any clinical trial, the results may be influenced if the patients who refuse to be studied differ in their characteristics from those who consent. This did not appear to be a major concern in this study, given the similarity of the base-line characteristics and the outcomes in the malnourished nonrandomized group and the study group. The low rate of complications in the well-nourished nonrandomized group as compared with the study group indicates that the nutritional criteria for eligibility effectively identified a high-risk population and that operative results that compare favorably with national norms can be achieved in the VA system in patients without extraordinary risk factors. The lack of such documentation in previous studies in high-risk populations of veterans has led to skepticism about the extrapolation of the results to non-VA populations.

The study group in this trial was determined to be malnourished on the basis of an objective nutritional assessment. From a nutritional perspective, these patients represented the worst 39 percent of the surgical candidates, identified after the exclusion of patients with major concurrent illnesses and a small group with clear-cut indications for preoperative TPN (3 percent of the patients in this study). The degree of malnutrition ranged from borderline to severe, with some patients appearing well nourished on the basis of the Subjective Global Assessment despite biochemical and anthropometric evidence of malnutrition. The effect of TPN on the operative outcome depended on each patient's base-line nutritional status. The therapeutic effects were divergent in the patients at the extremes of the spectrum of malnutrition represented by the study population.

Stratification according to nutritional status identified the patients with the most potential for harm and the most potential for benefit from TPN. Patients with mild malnutrition did not benefit from TPN but had more infectious complications. This finding was not explained by the presence of a catheter (that is, as a result of catheter sepsis or bacteremia), but instead it reflected a higher frequency of common postoperative infections (especially pneumonia and wound

infections). Nor do differences in the types of operations performed explain this observation, since procedures associated with an increased risk of infection (such as open-colon procedures) were performed more often in the control patients. It is unclear whether the use of TPN was causally related to the increased rate of infection. The TPN-treated patients were hospitalized longer (mean, five days) before surgery than the control patients, perhaps permitting colonization by resistant pathogens. Alternatively, a possible role for lipid in this process is suggested by the results of a trial by Muller et al.[6] in which the mortality of patients receiving preoperative lipid-based TPN was higher than that of patients receiving lipid-free TPN.

In contrast, there was no increase in the frequency of infections in the severely malnourished TPN-treated patients, but the frequency of noninfectious complications was significantly lower. These complications were primarily those indicative of the ability to heal wounds (anastomotic leaks or bronchopleural fistulae) and maintain normal organ function. This finding is consistent with the results of another study by Muller et al.,[7] which demonstrated reduced morbidity and mortality when TPN was provided before gastrointestinal surgery for cancer. The patients in that study were not selected on the basis of objective evidence of malnutrition, but they were nevertheless quite malnourished (mean serum albumin level, 35 g per liter), probably because of their underlying disease (64 percent had upper gastrointestinal cancer). Thus, they may approximate the severely malnourished group in this study.

The divergence in the findings of this trial depending on the patients' base-line nutritional status is also consistent with the results of a recent meta-analysis in which 18 studies of perioperative TPN were reviewed and the results of 11 studies that met adequate design criteria were pooled.[2] This analysis suggested a possible small benefit of TPN, but the 95 percent confidence intervals for the complication rates were wide. The authors concluded that any possible benefit of preoperative TPN in well-nourished patients was small and not clinically important, whereas efficacy in mildly or severely malnourished patients might be greater but would require further confirmation.

This study confirms the lack of benefit of TPN in borderline malnourished patients, provides strong evidence against clinically important efficacy in mildly or moderately malnourished patients, and suggests but does not confirm efficacy in severely malnourished patients. The severely malnourished population was small, representing less than 5 percent of the surgical candidates. These patients may be identified with a similar degree of confidence by careful Subjective Global Assessment or reliance on objective criteria. In the absence of severe malnutrition or other specific indications for preoperative TPN, most patients are probably best served by prompt surgery.

Appendix

The following persons participated in the VA Total Parenteral Nutrition Cooperative Study Group: Gordon P. Buzby, M.D. (study chairman), University of Pennsylvania School of Medicine; Gayle Blouin, M.D., University of South Carolina School of Medicine; Cindy L. Colling, R.Ph., M.S., VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center, Albuquerque, N.M.; Lon O. Crosby, Ph.D., Numedloc, Inc., Bryn Mawr, Pa.; Jeffrey E. Doty, M.D., Good Samaritan Hospital, Los Angeles; John M. Eisenberg, M.D., M.B.A., University of Pennsylvania School of Medicine; Gary F. Fitzpatrick, M.D., Boston University School of Medicine and Boston Veterans Affairs Medical Center (VAMC); John P. Grant, M.D., Duke University Medical Center; Linda S. Knox, R.N., M.S.N., University of Pennsylvania School of Nursing; James L. Mullen, M.D., University of Pennsylvania School of Medicine; Carey P. Page, M.D., Texas Health Science Center and Audie L. Murphy Memorial Veterans Hospital; Henry A. Pitt, M.D., Johns Hopkins Medical Institutions; Thomas Pollack, M.D. (deceased); John R. Potts, III, M.D., University of Texas Health Science Center at Houston; George F. Reinhardt, M.D., Department of Veterans Affairs (DVA) Hospital (Hines, Ill.), and Loyola University, Stritch School of Medicine; Thomas O. Rumley, M.D., University of Maryland and Johns Hopkins University; Hueldine Webb, M.D., Downstate Medical Center and Brooklyn VAMC; and William O. Williford, Ph.D., Cooperative Studies Program Coordinating Center, Perry Point, Md.

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