REVIEW ARTICLE

ANNALS OF SURGERY
Vol. 223, No. 4, 357–362

Protein-Sparing Therapy After Major Abdominal Surgery

Lack of Clinical Effects

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Objective
A prospective multicenter randomized trial was designed to evaluate the clinical efficacy of postoperative protein-sparing therapy.

Summary Background Data
The metabolic effect of postoperative protein-sparing therapy has been shown by several studies, but the clinical utility of this treatment has not been investigated by large prospective trials.

Methods
Six hundred seventy-eight patients undergoing major elective abdominal surgery were randomly assigned to receive either protein-sparing therapy after surgery (protein-sparing therapy group) or conventional therapy (control group). The patients were monitored for postoperative complications and mortality.

Results
The rate of major postoperative complications was similar in both groups (protein-sparing therapy group, 19.5%; control group, 20.9%; $p = 0.66$) as were the overall postoperative mortality rates (4.7% and 3.5%, respectively; $p = 0.43$).

Conclusions
The present study indicates that routine protein-sparing therapy for patients normonourished or mildly malnourished undergoing major abdominal surgery is not clinically justified.

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Accepted for publication May 9, 1995.

Although the nutritional efficacy of protein-sparing therapy (PST) has been shown,[1–3] the clinical use of this treatment has not been investigated by large prospective trials. The present study reports the results of a cooperative multicenter clinical trial designed to assess the efficacy of PST in patients normonourished or mildly mal-

Table 1. CRITERIA FOR THE EXCLUSION OF PATIENTS FROM THE STUDY

	No. of Patients
Patients with specific reason for exclusion*	343
Age <18 and >80 yrs	59
Major concurrent illness†	151
Cardiac	24
Neurologic	47
Hepatic	61
Renal	18
Pulmonary	9
Psychiatric	29
Insulin-dependent diabetes	29
Refusal of informed consent	47
Severe malnutrition‡	58

* The total of the specific exclusions shown below exceeds this number because some patients were included in more than one criterion.

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

‡ Patients were considered severely malnourished if the score by the nutritional risk index according to the following formula: 1.519 × the serum albumin level (in grams per liter) + 0.417 × (current weight/usual weight) × 100; was ≤83.5.[4,5]

nourished undergoing major abdominal surgery. The primary study objective was to determine whether PST reduces major postoperative complications, mortality, or both in such patients.

METHODS

The protocol of the study was approved by the Executive Committee of the Italian Society of Parenteral and Enteral Nutrition and by the ethical committees of the participating centers. Informed consent was obtained from the patients before entering the study.

All patients between the ages of 18 and 80 years who were admitted to surgical units of the participating centers from November 1992 to November 1994 and who were candidates for nonemergency abdominal surgery (excluding appendicectomy, cholecystectomy, and viscerolysis) were potentially eligible for the study. These patients were screened for any condition or conditions that would have made participation impossible or potentially dangerous or that could have had a substantial effect on the operative outcome, independent of treatment given; the criteria for exclusion are listed in Table 1. The patients who entered the study were randomly assigned by computer-generated random numbers to the PST group or the control group.

The patients in the PST group received 150 g glucose daily to meet the postoperative basal gluconeogenesis requirements plus 1.16 ± 0.22 g/Kg/day amino acids for at least 5 postoperative days. Additional fluids, electrolytes, vitamins, and trace elements were provided as clinically indicated.

The control patients received 150g glucose daily for at least 5 postoperative days. Additional fluids, electrolytes, vitamins, and trace elements were provided as clinically indicated.

Both PST and control patients received no oral intake for the first 5 postoperative days; thereafter, oral feeding could be instituted. In no case were parenteral fluids or hypocaloric nutrition continued for more than 7 postoperative days. In the case of "no realimentation" at postoperative day 8, total parenteral nutrition or tube feeding was instigated. Osmolarity of intravenous solutions ranged between 522.0 and 713.6 mOsm/L. Therefore, solutions could be administered safely by the peripheral route. However, if a central venous catheter had been positioned immediately before or during the operation for monitoring or fluid administration or both, it also was used during the postoperative course in both PST and control patients.

The patients were monitored for postoperative complications and mortality. Complications were classified by objective criteria as major or minor and also as infectious or noninfectious according to the following classification:

1. Major, Infectious
   a. Pneumonia: requires radiographic confirmation and documentation of pathologic organism in sputum and/or pleural fluid.
   b. Abdominal abscess: requires operative or spontaneous drainage of an abdominal purulent collection.
   c. Fascitis: requires surgical debridement of invasive fascial infection.
   d. Bacteremia: requires a clinical sign (either fever ≥38.5 C or shaking chill) and at least one positive blood culture of pathogenetic organisms.
   e. Septic shock: same as for bacteremia with arterial hypotension and/or hypoperfusion requiring pressor agents for hemodynamic maintenance.
   f. Septic coagulopathy: same as for bacteremia with demonstration of increased fibrin-split products at a 1:40 dilution and clinical evidence of bleeding.
2. Major, Noninfectious
   a. Anastomotic leak: requires documentation by re-operation or by contrast study of leak from suture line in a viscus into a body cavity or to the skin.
   b. Wound dehiscence: requires operative closure of the wound or results in incisional hernia at time of discharge.
   c. Gastro-intestinal complications:

(1) Bleeding: requires gastro-intestinal blood loss of sufficient magnitude to require transfusion of two or more units of blood in any 24-hour period for bleeding and operative or endoscopic documentation.
(2) Gastro-intestinal perforation, obstruction, and ischemia: requires operative, radiographic, or autopsy confirmation.
(3) Pancreatitis: clinical signs of pancreatitis confirmed by increase of serum or urinary amylase to at least twice the upper of normal (patients who satisfy the following conditions are excluded from this complication: pancreatitis on admission, previous long-term or relapsing pancreatitis, or endoscopic retrograde cholangiopancreatography on admission or operation on pancreas or biliary system that would provide adequate explanation for pancreatitis on a purely mechanical basis).

d. Cardiovascular complications:
(1) Myocardial infarction: requires standard clinical criteria with enzyme and/or appropriate electrocardiographic changes.
(2) Cardiogenic shock: requires hypotension and hypoperfusion necessitating pressor agents for > 60 minutes in the absence of sepsis or spinal cord injury.
(3) Cardiopulmonary arrest: requires temporary or permanent cessation of respiration and cardiac output sufficient to require both mechanical ventilatory support and external or internal massage.
(4) Stroke: development of a new and persistent (>48 hours) central neurologic deficit (excludes patients with severe anoxic brain damage due to hypoperfusion or anoxia).

e. Pulmonary embolus: requires documentation by pulmonary angiography or unequivocal lung scan.
f. Emoperitoneum: requires transfusion of six or more units of blood within the first 48 postoperative hours and/or re-exploration for bleeding within the first 7 postoperative days.
g. Pulmonary failure: requires the following conditions to be met: ventilatory support required for more than 24 hours postoperatively or reintubation required for ventilatory support within the first 7 postoperative days.
h. Renal failure:
(1) Grade I: rise in creatinine (Ames Company, Elkhart, IN) to >2.0 mg/dL or more above baseline (on-study values).
(2) Grade II: rise in creatinine to >5.0 mg/dL or twice baseline, whichever is higher, or initiation of peritoneal or hemodialysis.

3. Minor, Infectious
a. Wound infections: pus visible in wound.
b. Urinary tract infection: requires bacteriologic confirmation of >100.000 organisms/mL urine.
4. Minor, Noninfectious
a. Pleural effusion: requires radiographic confirmation.
b. Hepatic dysfunction: requires a postoperative rise in total serum bilirubin >2 mg/dL above on-study levels. Excluded from this complication are patients who undergo pancreatic or biliary tract procedures, have pre-operative bilirubin >2 mg/dL, are grossly jaundiced on admission, or have bilirubin rise because of mechanical obstruction.

Statistical Analysis

The primary objective for comparison was the incidence of major postoperative complications. Based on previous studies performed on our surgical population,[6] we anticipated a 20% incidence rate of major postoperative complications in the control group. A reduction of this rate by half (to 10%) in the PST 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 two-tailed test of proportions would require a total of 335 patients in each group. Thus, the goal for the accrual of patients was 675 for the final outcome analysis.

Continuous variables were compared by analysis of variance and categorical variables by the Fisher's exact test. Analysis of categorical covariates was performed by the Mantel–Haensel technique. All statistical analysis were two-tailed and were based on the intention-to-treat concept.

RESULTS

During the 24-month patient accrual, 1021 patients were identified as potentially eligible for the study. Of these, 343 patients (33.6%) were excluded for 1 or more of the reasons listed in Table 1; the remaining 678 patients consented to participate in the study and were randomly assigned to the PST group (n = 338) or the control group (n = 340). The PST group and the control group were similar regarding age, sex, nutritional status, and diagnosis as listed in Table 2.

All patients in the PST and control groups received short-term peri-operative prophylaxis. The extent of intra-operative contamination was comparable: no contamination in 214 (65.3%) and 222 (65.3%) patients (p = 0.59), mild contamination in 121 (35.8%) and 110

Table 2. BASE-LINE CHARACTERISTICS OF RANDOMIZED PATIENTS

	PST Group	Control Group	Both
No. of patients	338	340	678
Age (yrs)	61.1 ± 10.8	61 ± 10.5	61 ± 10.6
Sex (M/F)	205/133	187/153	392/286
Nutritional status			
Body weight (kg)	68.5 ± 11.9	68 ± 12.1	68.3 ± 12
% Usual weight	97.7 ± 5.2	98.4 ± 4.6	98 ± 5.0
Serum albumin (g/dL)	4.03 ± 0.57	3.9 ± 0.51	4.01 ± 0.54
Serum transferrin (mg/dL)	260 ± 55.6	265 ± 61.2	263 ± 58.5
No. of mildly malnourished patients	80	67	147
Diagnosis			
Gastric cancer	52	58	110
Colorectal cancer	199	196	395
Pancreatic cancer	12	11	23
Other GI cancer	4	6	10
Benign GI disease	26	28	54
Other	45	41	86

PST = protein-sparing therapy; GI = gastrointestinal.

(32.3%) patients (p = 0.34), severe contamination in 3 (0.9%) and 8 (2.3%) patients (p = 0.13), respectively.

Table 3 lists the operative procedures undergone by the 338 patients receiving PST in the PST group and 340 patients in the control group.

Intravenous solution was infused through a central venous catheter in 95 (28.1%) and 108 (31.8%) patients in the PST and control groups, respectively (p = 0.29); in the remaining 243 (71.8%) and 232 (68.2%) patients, respectively, the peripheral route was adopted.

Sixteen of the 338 patients assigned to the PST group (4.7%) and 12 of the 340 assigned to the control group (3.5%) died during the postoperative period. The difference is not statistically significant (p = 0.43).

The rates of major postoperative complications were similar in the two groups: 66 of the 338 patients receiving PST (19.5%) and 71 of the 340 control patients (20.9%) had such complications (p = 0.66). The overall rates of postoperative complications (major or minor) were 31.1% and 34.1%, respectively (p = 0.39).

There were no differences between the PST and the control groups when both major infectious and noninfectious complications are considered, the rates being 7.7% *versus* 5% (p = 0.15) and 15.1% *versus* 17.4% (p = 0.42), respectively. The rates of individual complications and the relative risk and confidence intervals are listed in Table 4.

When patients mildly malnourished (n = 147) were considered separately, the rates of major postoperative complications and postoperative mortality resulted as being comparable in the PST group and the control group, 22.5% *versus* 29.9% (p = 0.31) and 8.8% *versus* 7.5% (p = 0.77), respectively.

There were more, but not significantly more, major infectious complications in the PST group than in the control group (11.3% *vs.* 6%, p = 0.26) and slightly more major noninfectious complications in the control group (20% *vs.* 26.9%, p = 0.32). The rates of individual complications and the relative risk and confidence intervals in patients mildly malnourished are listed in Table 5.

DISCUSSION

Surgery of the digestive tract involves, in addition to the usual stress of an operation, interruption of the natural nutritional mechanism for a variable time. Even in patients who are normonourished, postoperative fasting quickly exhausts the carbohydrate store, leading to use of the protein compartment as an alternative source of energy.[7]

The infusion of exogenous amino acids and carbohydrates as PST, also called hypocaloric parenteral nutrition, aims to counteract the increased protein losses. This system of parenteral nutrition is adapted specifically to the requirements of postoperative metabolism. An adequate caloric supply through parenteral nutrition is not the objective of the procedure; on the contrary, the dosage of carbohydrates is consciously kept to a minimum. Therefore, the condition for effective application of PST is that the organism is able to meet the energy demands itself by mobilizing endogenous reserves.

Severe malnutrition or the necessity for long-term parenteral nutrition consequently does not provide a foun-

Table 3. OPERATIVE PROCEDURES PERFORMED IN THE RANDOMIZED PATIENTS

Type of procedure	PST Group	Control Group	Both
Esophagectomy	2	1	3
Total gastrectomy	30	26	56
Distal subtotal gastrectomy	30	37	67
Colon resection	106	100	206
Subtotal colectomy	22	15	37
Anterior resection of rectum	67	62	129
Abdomino perineal excision of the rectum	16	19	35
Restaurative proctocolectomy	5	2	7
Small bowel resection	4	3	7
Pancreatoduodenectomy	11	10	21
Biliodigestive anastomosis	6	10	16
Other	39	55	94
All procedures	338	340	678

PST = protein-sparing therapy.

Table 4. POSTOPERATIVE COMPLICATIONS*

Type of Complication	PST Group (n = 338)	Control Group (n = 340)
Major infectious		
Pneumonia	14	9
Abdominal abscess	6	1
Fasciitis	1	0
Bacteriemia		6
Other septic complications	3	2
Total	31	18
No. of patients affected (%)	26 (7.7)	17 (5.0)
Relative risk (PST: control) = 1.02		
95% Confidence interval = 0.98–1.07		
Major noninfectious		
Anastomotic leak	20	18
Wound dehiscence	10	3
Gastrointestinal complications†	11	23
Cardiovascolar complications‡	6	6
Pulmonary embolus	2	1
Emoperitoneum	4	5
Pulmonary failure	1	2
Renal failure	2	3
Total	56	61
No. of patients affected	51 (15.1)	59 (17.4)
Relative risk (PST:control) = 0.97		
95% Confidence interval = 0.91–1.04		
Minor infectious		
Wound infections	19	23
Urinary tract infection	22	18
Minor noninfectious		
Pleural effusion	17	16
Hepatic disfunction	5	6

PST = protein-sparing therapy.
* The total number of patients shown for major complications is less than the sum of the patients listed as having individual complications because many patients had more than one complication.
† Includes bleeding, obstruction, perforation, ischemia and acute pancreatitis.
‡ Includes myocardical infarction, cardiogenic shock, cardiopulmonary arrest, and stroke.

Table 5. POSTOPERATIVE COMPLICATIONS IN MILDLY MALNOURISHED PATIENTS*

Type of Complication	PST Group (n = 80)	Control Group (n = 67)
Major Infectious		
Pneumonia	6	2
Abdominal abscess	3	0
Bacteriemia	2	1
Other septic complications	3	1
Total	14	4
No. of patients affected (%)	9 (11.3)	4 (6)
Relative risk (PST:control) = 1.05		
95% Confidence interval = 0.96–1.16		
Major noninfectious		
Anastomotic leak	8	6
Wound dehiscence	3	0
Gastrointestinal complications†	3	7
Cardiovascolar complications‡	1	2
Emoperitoneum	1	1
Pulmonary failure	0	1
Renal failure	1	2
Total	17	19
No. of patients affected (%)	16 (20)	18 (26.9)
Relative risk (PST:control) = 0.91		
95% Confidence interval = 0.76–1.09		
Minor infectious		
Wound infections	7	6
Urinary tract infection	4	5
Minor, noninfectious		
Pleural effusion	7	3
Hepatic disfunction	1	1

PST = protein-sparing therapy.
* The total number of patients shown for major complications is less than the sum of the patients listed as having individual complications because many patients had more than one complication.
† Includes bleeding, obstruction, perforation, and ischemia.
‡ Includes myocardical infarction, cardiogenic shock, cardiopulmonary arrest, and stroke.

dation for the application of this system. For this reason, the present study randomized only normonourished or slightly malnourished surgical patients in which the duration of expected nothing by mouth period was no longer than 7 days.

Although some studies have shown the metabolic efficacy of PST in postoperative surgical patients,[1–3] to our knowledge the clinical effect of this regimen has not been investigated by large prospective trials. The results of the present study showed no significant reduction of morbidity and mortality when PST was compared with conventional fluid therapy. Even subdividing postoperative complications into different types (infectious and noninfectious, minor and major), we observed no statistically significant differences between treated and control patients.

Moreover, in the subgroup of patients identified as mildly malnourished, PST did not have a significant impact on postoperative outcome.

In conclusion, the present study indicates that routine PST nutrition for normonourished or mildly malnourished patients undergoing major abdominal surgery is not justified from a clinical point of view.

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Appendix

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