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The Effect of Postoperative Intravenous Feeding (TPN) on Outcome Following Major Surgery Evaluated in a Randomized Study

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Three hundred patients undergoing major general surgical procedures were randomized by means of a computer-assisted algorithm to receive either total parenteral nutrition (TPN) from the first postoperative day or only prolonged glucose administration (250–300 g/day) up to 15 days after operation. All patients receiving TPN were treated individually based on daily measurements of energy and nitrogen balances. The treatment goal was to keep the patients in positive energy balance (+20%) and close to nitrogen balance. The effects of the two "nutrition regimens" on outcome such as mortality rate, complications, the need of additional medical support and patient-related functional disabilities were investigated. No selection of patients was made, that is, malnourished patients were also randomized. There were no differences among TPN *versus* glucose treatment when results were analyzed according to intent to treat. Approximately 60% of all patients were able to start eating within 8 to 9 days after operation. No differences were observed between such patients regardless of being treated with TPN or glucose only. Patients on glucose treatment during 14 days had a significantly higher mortality rate ($p < 0.05$) than patients on either continuous and uncomplicated TPN treatment or short-term glucose treatment. Similar results for mortality rates also were seen with regard to severe complications (cardiopulmonary problems, sepsis, and wound-healing insufficiencies), functional disturbances, the need of additional medical support, and abnormalities in nutritional state. Twenty per cent of the patients randomized to TPN treatment showed a statistical trend ($p < 0.10$) toward a higher mortality rate (36%) compared with patients randomized to prolonged glucose treatment (21% mortality rate). These patients could not be identified by evaluation of preoperative factors. Thus, the overall evaluation of the results makes it likely that a fraction of high-risk patients ($\approx$20%) were not doing well on immediate postoperative intravenous feeding, and it is possible that TPN to such patients accentuated their morbidity rate. Although patients (20%) on prolonged semi-starvation (14 days glucose treatment) had increased mortality rate and severe complications, it was possible that undernutrition induced a slightly different complication scenario than induced by TPN in the high-risk patients. The results demonstrate that in most surgical patients (60%), postoperative semi-starvation is not a limiting factor for outcome. In remaining 40%, inadequate nutrition was associated with both increased morbidity and mortality rates. In this sense, inadequate nutrition represents both too much and too little, whereas overfeeding seemed to be a larger problem than underfeeding. Based on results in the current study, we propose that TPN represents a life-saving modality in approximately 20% of unselected patients undergoing major surgical procedures. Unfortunately, these patients are so far not possible to identify by preoperative criteria.

It is well known that undernutrition before operation is associated with decreased performance and a prolonged hospital stay because of a higher complication rate in patients undergoing demanding medical treatments, including surgery.[1-4] This fact has led to the assumption that early nutritional intervention would improve treatment outcome and decrease the number of serious complications, not only in patients with manifest undernutrition, but also in patients with only incipient malnutrition.[5-7] Because biochemical signs of malnutrition are appearing rapidly after operation, it also has been suggested that immediate or early institution of postoperative nutrition should benefit the patient.[8] Many institutions have adopted early postoperative nutrition on a routine basis at high cost after major surgery based on facts from the nutrition-related physiology and on findings in some previous uncontrolled studies.[6,8] The role of early postoperative nutrition is still unclear, irrespective of whether patients are malnourished. Therefore, the aim of this study was to investigate whether immediate institution of total parenteral nutrition in the postoperative course is of benefit for the patient compared to prolonged use of only glucose/electrolyte administration to unselected patients after major surgery.

MATERIAL AND METHODS

Patients and Inclusion–Exclusion Criteria

This study started to recruit patients in October 1987 and it was finished in December 1989. Subjects were included from six surgical wards and one urology ward. Patients undergoing acute or elective major surgical procedures were eligible. Patients with acute multiple trauma, treated in the intensive care unit, also were qualified even without expected operation. Minor surgical procedures were the only exclusion criteria. The patients were randomized according to Simon and Pocock[9] by means of a computer-based algorithm stratifying for sex, age, type of surgery, nutritional state, operation time, blood loss, experience of the surgeon, the particular ward the patient were treated in, complicating factors, and "physiologic associated variables." Complicating factors were diabetes, cardiac arrhythmia, hypertension, vascular and coronary disease, smoking habits, cancer disease, kidney function, history of pulmonary disease, cortisone treatment. Physiologic variables were: maximum air peak flow, hand-grip strength, walking-time in standard stairs, the rise in the pulse rate during climbing the standardized stairs, and estimation of resting fatigue by means of a visual analog scale. Most of the randomization variables were collected before operation and some immediately after operation. The randomization was performed the operation day.

Nutrition Treatment

Practical procedures that were required for total parenteral nutrition (TPN) treatment were carried out in the afternoon after randomization. Treatment started at 7:00 A.M. the next morning (the first postoperative day). The patients were randomized to receive continuously either complete intravenous nutrition (TPN, group 1) or only plain D-glucose (group 2) with standard electrolytes (glucose-group) until the patient had recovered enough to drink or eat freely without any need of parenteral fluid or electrolyte support. This judgment and decision were made on clinical grounds by the physician in charge entirely independent of the study team. The intravenous nutrition was prescribed according to the patient's daily individual need based on daily measurements of energy expenditure and total nitrogen excretion. The non-protein energy corresponded to 120% of the measured energy expenditure. Nitrogen was given to cover all nitrogen losses according to the measured nitrogen losses the day before, because it is not known what the optimal provision of nitrogen is in unselected patients in the presence of different levels of stress, various body compositions, and provision of plasma and blood products in the perioperative period (Fig. 1B). Nonprotein calories consisted of 70% carbohydrate (D-glucose) and 30% lipids (20% Intralipid, KabiVitrum, Stockholm, Sweden). Nitrogen was given as crystalline amino acids (Vamin 9, Vamin 14, Vamin 18, KabiVitrum), depending on the level of nitrogen requirement. The total amount of amino acid supply generally did not exceed 18 to 20 g nitrogen/day. Vitamins (Soluvit, Vitalipid), electrolytes (Na, K, Mg, phosphates), and trace elements (Addamel) were given according to daily defined and minimum requirements.[10] The intravenous nutrition was given as recommended by the manufacturer, that is, lipids and amino acids were infused simultaneously through the same central line during the day and the glucose was given during the night. Values for energy expenditure and nitrogen losses were put into a computer for calcula-

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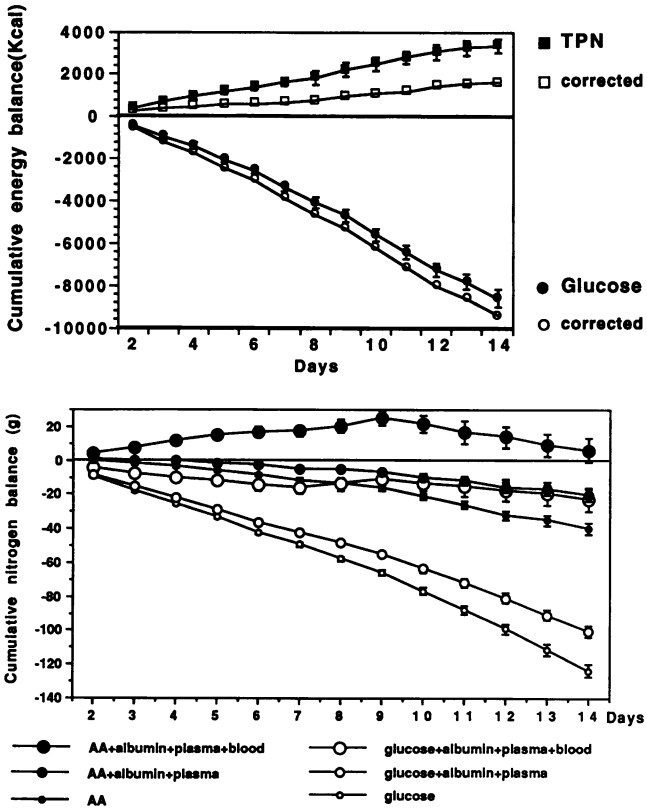

Figure 1. (A, top) Apparent cumulative energy balance when results were calculated according to intent to treat. Similar charts were obtained when computations were performed according to actual treatment. "Corrected" refers to energy balance accounting for the loss of glucose in urine. (B, bottom) Cumulative nitrogen balance when results were computed according to intent to treat. Similar charts were obtained when computations were performed according to actual treatment. The nitrogen balances become different whether protein substitutes are included or not. The various alternatives are illustrated.

tion of the individual nutrition requirement of each patient every day throughout the study. Patients randomized to glucose treatment (group 2) were decided to receive 250 to 300 g D-glucose per day, which was considered the minimal daily requirement for the central nervous system. This amount was provided as 10% to 20% glucose solutions with electrolytes according to measured needs. The study and the control nutrition regimens went on until the patient could drink freely. If a patient randomized to glucose treatment could not drink or eat freely on day 15, this was regarded as a therapeutic failure in the "glucose-arm" and the patient was transferred to TPN according to the principals for the "TPN-arm" until freely eating was possible (group 3). In a pilot study, this "glucose-time period" was first set to 3 weeks instead of 2 weeks based on theoretical calculations where threatening complications to upcoming undernutrition should occur to a significant extent. An applied test period, however, showed that few patients who had not started to eat within 15 days generally did not do so within 21 days. It also was registered that the appearance of malnutrition seemed to be accelerated between 2 and 3 weeks compared with 1 to 2 weeks after operation. Therefore, the protocol was changed accordingly.

If metabolic or circulatory complications occurred that made the prescribed complete intravenous nutrition impossible to fulfill, the patient was transferred to a new group with patients in whom TPN treatment was insufficient or problematic (group 4). Such complications could be acute cardiac and pulmonary insufficiency, progressive kidney dysfunction, etc. The intravenous nutrition in this group was principally according to the original protocol with daily modifications judged necessary based on clinical grounds. Such modifications could be reduction in energy and nitrogen supply; reduction or omission of fat supply; a change from standard amino acid solutions to solutions with only essential amino acids, etc. The decision to transfer a patient from group 1 to group 4, and the prescription of nutrition to patients in group 4, was decided by the nutrition team.

Medical treatments such as antibiotics, colloides (albumin, blood, plasma), and crystalline substitutions were prescribed according to the patient's need by the clinician in charge based on clinical evaluation and routine procedures.

Metabolic and Biochemical Monitoration

Daily measurements of nitrogen and energy metabolism were performed. Energy expenditure was measured during 30 minutes between 9:00 and 12:00 A.M. by mobile computerized equipment (Deltatrac, Datex, Finland) each day in all patients. Urine output, fecal losses, and all other body fluids (gastric, wound, and drain fluid) were collected daily and prepared for measurements of nitrogen content with a chemoluminescence technique (Antek Instruments, Inc., Düsseldorf, Germany). Liver and kidney function tests and nutritional status were carried out twice a week.

Follow-up Measurements

The day after finishing the nutrition or glucose therapy several end-point measurements were carried out to evaluate the functional outcome in the study and control groups. Such measurements were: resting energy expenditure after an overnight fast, all the nutritional variables that were measured before operation (see above), and some additional variables (pulse rate, total body potassium, prealbumin, retinol-binding protein, thyroid hor-

mones). Outcome variables in the study consisted of: total hospital stay, theoretical hospital stay, which was the time point when the patient was judged by the nutrition nurses (U.K, M.G) as being capable of leaving the hospital for medical reasons, the time period with an intravenous line, the time in the intensive care unit, the time with ventilator support, the time with obligatory need of extra oxygen supply according to blood gas analyses, and severe complications (myocardial infarction thrombosis, sepsis, etc.). All additional medical support during the whole nutrition period was also registered for evaluation. In addition, we evaluated a set of "functional variables" that we associated with patient's quality of life. Such variables were: the time period in days it took the patient to be able to get adequate contact with family members and the ward staff; to be able to take care of personal hygiene; walk to the toilet with minimum support; need for urinary bladder catheter; take care of intestinal stomas by themselves without nurse support; read a book; listen to the radio; attend TV programs in the ward TV room; walk in a standard stairs between two wards; and the time it took to climb the standard stairs.

Statistics

Values are given as mean ± standard error. Firstly, data computation was performed strictly according to the randomization, which is referred to as intent to treat.[11] Secondly, analyses were carried out according to censored patients, who could not fulfill the prescribed treatment, which is referred to as actual treatment.[11] Differences between two groups were analyzed with the Student t test. Differences among several groups were tested by analysis of variance. Repeated measurements over time within and between groups were tested by analysis of variance for repeated measures. Whether the number of patients and complications differed between groups were tested by contingency table chi square analyses with continuity correction. Probability values of $p < 0.05$ with two-tailed tests were considered significant.[12] In most tables where we have tested differences among groups 1 through 4, we only indicate post-hoc significance between group 1 (TPN) and group 3 (glucose to TPN) and between group 3 and group 4 (complicated TPN). Some indications are also made for trend probabilities in presentation of mortality rates and complications (Table 8). This study was not planned to test the hypothesis whether mortality rates differ between TPN and glucose treatments, which would have demanded around 2000 randomized patients according to prestudy estimations and expected frequencies in overall mortality rates of 6% to 7% and a 30% to 50% improvement by nutrition. Instead, treatment outcome and functional variables were the test parameters in this study. For this purpose, estimates of the required number of patients were usually 40 to 60 patients, depending on different variables. Therefore, it was decided to include 300 randomized patients for subsequent possibilities to consider the results in expected subgroups, which should take approximately 3 years in our institution.

Table 1. OUTCOME OF RANDOMIZATION: INTENT TO TREAT

	Total Parenteral Nurtrition	Glucose
No. of patients:	150	150
Sex		
M	94	94
F	56	56
Age distribution (yr)		
20–25	0	1
26–30	0	1
31–35	7	5
36–40	1	0
41–45	6	3
46–50	6	6
51–55	7	10
56–60	19	20
61–65	21	19
66–70	29	31
71–75	33	19
76–80	12	26
81–85	6	8
86–90	3	1
Average age		
M	64 ± 4	65 ± 4
F	64 ± 4	64 ± 4
Type of surgery		
Cystectomy	19	19
Hepatic-pancreatic operation	35	33
Intestinal surgery	22	20
Major vascular surgery	42	44
Gastro-esophageal operation	32	32
No operation	0	2

Before the study started in 1987, it was discussed and approved by all senior surgeons and anesthesiologists in charge of patients entering the study. The protocol was approved by the Committee for Ethics at the Medical Faculty, University of Göteborg, Sweden. All patients gave informed consent before operation or they were informed at their earliest convenience when included as acute patients. No patient refused to continue according to the protocol and planned procedures when informed after randomization.

RESULTS

Randomization

The computer-based algorithm provided a study and a control group that were almost identical in stratification

variables (Tables 1 and 2). Thus, the two groups did not differ statistically in any measured respect before nutrition. The group vascular surgery included 51 acute or elective aortic aneurysm and 7 cases of surgical operations on the visceral arteries, the remaining being occlusive aortic lesions and portosystemic shunting operations. Gastroesophageal operations included 23 total gastrectomies, the rest (n = 41) being subtotal gastrectomies with esophageal reconstructions or gastric operations with thoracoabdominal approaches. Cystectomies were performed followed by reconstruction according to Bricker in all cases. The intestinal surgery group contained mainly abdominoperineal large bowel resections with or without pouch reconstructions (n = 20), the rest (n = 22) being major small-bowel resections due to inflammatory bowel disease. Hepatic–pancreatic operations included 13 total or subtotal pancreatectomies, 16 right liver lobe resections, 8 left liver lobe resections, and 9 nonclassic hepatectomies, which were mainly extended lobe resections, 9 bilio-digestive shunts (Longmire operation), and 13 miscellaneous cases, generally extended resections *en bloc,* including several organs and retroperitoneal tumor.

Twenty-eight patients randomized to TPN did not tolerate the therapy according to the protocol (group 4). Twenty-four patients randomized to the glucose group were transferred to TPN therapy after 14 days on glucose therapy only according to the protocol (group 3), because they were unable to start eating within 15 days. This group of patients could start freely eating at 20 ± 4 days after operation, which was significantly later compared with patients on uncomplicated TPN and glucose treatment (groups 1 and 2; 9 ± 1 and 8 ± 1 days, respectively).

Nutrition Treatment

The treatment goal to keep study patients in positive energy balance was reached, although glucosuria appeared in a large number of patients without overt diabetes (Fig. 1A). It was also difficult or impossible to keep patients in nitrogen balance (Fig. 1B). The precise degree of nitrogen balance may be different depending on whether obligatory substitutes for circulatory support (blood, plasma, albumin) are included in balance calculations or not (Fig. 1B).[13] Thus, patients on uncomplicated TPN (group 1) had 105 ± 3% of their resting energy expenditure covered and patients on glucose treatment (group 2, group 3) had only 65 ± 4% supplied, whereas patients in the TPN group (group 4), who did not tolerate prescribed energy intake, received only 80 ± 4% of their daily resting energy expenditure as compared with their prescribed 120%.

Nutritional and Functional Variables

Nutritional variables, hemoglobin concentration, serum creatinine, and erythrocyte sedimentation rate at admission were similar in the study and the control group without any unexpected outfall (Table 3). Serum albumin before operation was significantly decreased in both groups, probably reflecting both the degree of disease state and undernutrition. The mean weight loss was 9% to 10% in both groups, with a range of 3% to 29%. Of randomized patients, several could thus be regarded as being either incipiently or manifestly malnourished, depending on the definition of malnutrition. The most simple definition, namely, weight loss exceeding 3% of their normal body weight, showed 70 patients in the TPN group and 72 patients in the glucose group to be poten-

Table 2. ADMISSION VARIABLES USED IN RANDOMIZATION AS STRATIFICATION VARIABLES: INTENT TO TREAT

	Total Parenteral Nutrition	Glucose (n = 150)
Operation performed		
Acute	16	16
Semi-acute	5	6
Elective	128	128
Duration of operation (min)	332 ± 10	316 ± 11
Bleeding during operation (mL)	1876 ± 129	1862 ± 151
Complicating factors		
Diabetes	12	11
Hypertension	44	29
Vascular disease	53	56
Smoking	41	43
Cancer	97	88
Cortisone treatment	4	9
Total of complicating factors	251	236

Table 3. NUTRITIONAL AND BLOOD CHEMICAL VARIABLES AT ADMISSION*

	Total Parenteral Nutrition (n = 150)	Glucose (n = 150)
Weight (kg)	70.3 ± 1.1	70.0 ± 1.2
Weight reduction (%)	8.3 ± 2.0	8.7 ± 2.0
Resting energy expenditure (kcal/day)	1686 ± 31	1668 ± 26
TSF (mm)	13.3 ± 0.5	13.7 ± 0.9
Arm circumference (cm)	29.2 ± 0.3	29.2 ± 0.3
Leg circumference (cm)	51.4 ± 0.5	51.3 ± 0.5
Albumin in serum (g/L)	27.9 ± 1.5	26.8 ± 1.2
Protein in serum (g/L)	62.9 ± 1.1	59.6 ± 1.9
Hemoglobin concentration (g/L)	130 ± 1.5	132.6 ± 2.7
Serum creatinine (μmol/L)	108 ± 5	99 ± 3
Erythrocyte sedimentation rate (mm/hr)	24 ± 2	27 ± 2

* These parameters served as stratification variables in randomization: intent to treat.
TSF, triceps skinfold.

tial weight-losers. Severe weight losers with more than 10% weight loss during the preceding 3 to 6 months before operation were 30 and 37 patients in the TPN and glucose groups, respectively. Most of these patients (70%) belonged to the gastroesophageal and hepatico-pancreatic operation groups. If 2 or 3 indices of subnormal nutritional variables were combined to reflect manifest undernutrition, 60 to 80 patients of 300 were defined to be manifestly malnourished in the TPN/glucose groups together, without any difference between the study and control group.

The effect of TPN on nutritional status was minor only when analyzed according to intent to treat (Table 4). Retinol binding protein was significantly improved in the TPN group and T_4 and free T_3 were lower in the TPN group (results not shown). Several significant differences were found when results were analyzed according to actual treatment, however (Table 4). Such differences were usually dependent on differences between group 1 and group 2 (uncomplicated treatments) *versus* group 3 and group 4 (complicated treatments). Glucose treatment induced an adaptation to starvation, which was seen as significantly lower energy expenditure, lower nitrogen excretion (Fig. 2), decreased body temperature and pulse rate in glucose-treated (group 2) *versus* TPN-treated (group 1) patients (Table 5). Prolonged glucose treatment (group 3) was associated with significantly lower tissue-coding factor, arm muscle circumference, leg circumference, and plasma T_4 compared with TPN-treated patients in group 1. Some nutritional indexes were higher in group 4 compared with group 3 (arm and leg-circumference, retinol binding protein), which may indicate that even modified TPN had some protective effects

Table 4. NUTRITIONAL STATUS AT THE END OF THE STUDY PERIOD: ACTUAL TREATMENT

	Total Parenteral Nutrition gr 1 (122)	Glucose gr 2 (126)	gr 3 (24)	gr 4 (28)	ANOVA p
Body weight (kg)	65.3 ± 1.3	66.4 ± 1.4	60.9 ± 1.0*	60.6 ± 1.0	<0.0032
Resting energy expenditure (kcal/day)	1747 ± 31	1625 ± 25†	1607 ± 77*	1658 ± 110	<0.01
Body temperature (C)	37.7 ± 0.05	37.4 ± 0.05†	37.7 ± 0.2	37.6 ± 0.11	<0.001
Pulse rate (beats/min)	98 ± 1	88 ± 1†	84 ± 2*	97 ± 1‡	<0.0001
TSF (mm)	13.1 ± 0.6	12.5 ± 0.5	9.1 ± 0.6*	12.6 ± 1.4	<0.05
Arm circumference (cm)	28.8 ± 0.3	28.7 ± 0.3	25.2 ± 1.1*	28.2 ± 0.9‡	<0.007
Leg circumference (cm)	51.0 ± 0.5	50.3 ± 0.5	46.5 ± 1.3*	50.9 ± 0.9‡	<0.04
TBK (mmol)	2884 ± 82	2794 ± 80	2689 ± 100	2727 ± 244	
Albumin (g/L)	29.3 ± 0.5	30.5 ± 0.5	26.9 ± 1.3	29.8 ± 1.9	
Pre-albumin (g/L)	0.16 ± 0.009	0.16 ± 0.007	0.12 ± 0.01	0.16 ± 0.02	
Retinol (g/L)	56.2 ± 2.7	51.3 ± 2.2	43.9 ± 5.3	78.0 ± 14.2‡	<0.02
Free thyroxine (pmol/L)	11.2 ± 0.3	13.7 ± 1.2	9.4 ± 1.0	9.7 ± 0.8	
TSH (nmol/L)	3.0 ± 0.6	2.8 ± 0.3	5.5 ± 1.5	2.8 ± 1.0	
T3 (nmol/L)	1.5 ± 0.1	1.5 ± 0.4	1.3 ± 0.1	1.2 ± 0.09	
T4 (nmol/L)	90.8 ± 2.2	102.0 ± 2.1	74.7 ± 7.6*	78.8 ± 4.4	<0.0001
Free T3 (nmol/L)	3.0 ± 0.1	3.3 ± 0.1	2.6 ± 0.3	2.3 ± 0.3	<0.006
Reversed T3 (nmol/L)	0.48 ± 0.2	0.54 ± 0.02	0.39 ± 0.06	0.42 ± 0.04	

* $p < 0.05$ gr 1 *versus* gr 3.
† $p < 0.05$ gr 2 *versus* gr 1.
‡ $p < 0.05$ gr 3 *versus* gr 4.
TSF, triceps skinfold; TBK, total body potassium; TSH, thyroid stim hormone.

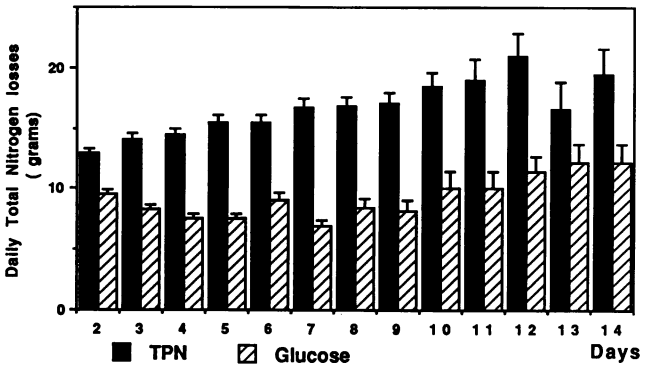

Figure 2. The daily total nitrogen loss (including urinary nitrogen, wound fluid, gastrointestinal secretion, and excretion) in all patients when calculated according to intent to treat. A similar chart was obtained if calculation was performed according to actual treatment.

on the nutrition state, but this may have been obtained to the price of an increased heart load indicated by a significantly higher pulse rate (97 beats/minute *versus* 84; $p < 0.05$) associated with morbidity.

Functional and physiologic variables were not different in any respect between the study and control groups at admission before operation (Table 5). When analyzed according to intent to treat at the end of the study period, 7 of 14 such variables were significantly worse in the entire TPN group compared with the entire group with glucose-treated patients (adequate contact, personal hygiene, walk to toilet, read a paper, listen to the radio, attend TV programs, walk the standard stairs) (results not shown). None of these variables was significantly worse in the glucose-group compared with the TPN group. When analyzed according to actual treatment, however, none of these seven variables remained significantly worse in the TPN group (group 1), compared with the control group (group 2) (Table 6). Thus, these problems with TPN were entirely dependent on poor results in the complicated TPN-group (group 4), and on patients on prolonged glucose treatment (group 3) (Tables 5, 6). It is important to emphasize that patients in group 4 had several functional variables that indicated a more deteriorated function than that seen in group 3 (Tables 6, 7, 8). Additional outcome variables again showed a significantly worse outcome in group 3 and group 4 compared with group 1 and group 2 (Table 7), including prolonged theoretical and actual hospital stay. Group 3 (glucose to TPN) did significantly worse in several aspects (hospital stay, need of IV line, intensive care unit treatment, need of extra oxygen, time period with abnormal blood gases) compared with uncomplicated TPN-patients (group 1) and short-term treated glucose-patients (group 2). The need of additional treatments was comparable in the both groups when analyzed according to intent to treat. The demand for insulin, antibiotics, blood, plasma, and colloid substitutions, however, were again significantly larger in group 3 (glucose to TPN) compared with the uncomplicated TPN group (group 1) (Table 7). Patients in group 4 (modified TPN) had a significantly larger demand for ventilator support and extra oxygen supply compared with patients with prolonged glucose treatment (group 3) (Table 8).

Mortality and Complications

The overall mortality rate (7.3%) during the hospital stay was not different between TPN and glucose treatments, when analyzed according to intent to treat. The mortality rate was significantly different among groups 1 to 4, which was due to a very high mortality rate in group 3 (21%) and group 4 (36%) (Table 8). This pattern also was seen with regard to other serious complications (myocardial infarction, myocardial insufficiency, arrhythmia, thrombosis, suture insufficiency, sepsis, arrhythmia). The uncomplicated TPN group (group 1) did not differ in any respect to the short-term glucose group (group 2), although the mortality rate was threefold higher ($p < 0.15$) in glucose-treated patients (group 2) *versus* TPN-treated patients (group 1). There was also a trend to a higher mortality rates in group 4 *versus* group 3 ($p < 0.10$), and this trend reached statistical significance with regard to myocardial insufficiency ($p < 0.05$). Because of the poor outcome in group 4, overall recalculations were performed with exclusion of patients in group 4 (Table 8). This indicated that mortality rate still was significantly higher in group 3 (glucose to TPN) compared with both group 1 and group 2. This was also true for the occurrence of thrombosis, wound rupture, sepsis, and cerebral dysfunctions ($p < 0.05$).

A final analysis on surviving patients did not confirm a different need for home *versus* continuous institutional care during the convalescence among the patient groups. There seemed to be a trend to a larger need of ambulance transportation in both group 3 and group 4, however, when leaving the hospital (Table 9).

Table 5. PHYSIOLOGIC RELATED VARIABLES AT ADMISSION*

	Total Parenteral Nutrition (150)	Glucose (150)
Air peak flow (L/min)	288 ± 16	274 ± 16
Handgrip strength (kg)	23.3 ± 1.2	22.7 ± 1.3
Walking time on defined stairs (sec)	4.1 ± 0.3	7.4 ± 3.3
Fatigue visual analog scale (units, 0–10)	2.7 ± 0.2	2.7 ± 0.2

* These parameters served as stratification variables in randomization: Intent to treat.

Table 6. FUNCTIONAL (days) AND PHYSIOLOGIC VARIABLES AT THJE END OF THE STUDY PERIOD: ACTUAL TREATMENT

	Total Parenteral Nutrition gr 1	Glucose gr 2	gr 3	gr 4	ANOVA p
Adequate contact	2.6 ± 0.3	2.6 ± 0.2	2.2 ± 0.2	11.9 ± 4.3*	<0.0001
Personal hygiene	4.9 ± 0.4	4.2 ± 0.2	6.1 ± 1.1†	12.2 ± 3.2*	<0.0001
Walk to the toilet	6.5 ± 0.5	5.3 ± 0.2	6.3 ± 0.5	15.7 ± 4.4*	<0.0001
CAD days	7.0 ± 0.5	7.3 ± 1.1	13.3 ± 3.4†	21.5 ± 4.3*	<0.0001
Take care of stoma	17 ± 2	18 ± 3	31 ± 11	23 ± 9	
Read a book	6.9 ± 0.9	7.0 ± 1.1	9.7 ± 2.3	9.3 ± 2.4	
Read a newspaper	5.8 ± 0.5	5.2 ± 0.3	5.4 ± 0.5	13.9 ± 3.5*	<0.0001
Listen to radio	5.8 ± 0.5	5.0 ± 0.3	7.2 ± 1.1	13.6 ± 3.7*	<0.0001
Watch television	7.1 ± 0.8	6.6 ± 0.4	7.1 ± 0.7	19.4 ± 4.0*	<0.0001
Walk stairs	11.7 ± 0.6	10.8 ± 0.5	17.3 ± 2.1†	26.8 ± 5.6*	<0.0001
Air peak flow (L/min)	263 ± 11	265 ± 11	197 ± 25	260 ± 28	
Walking time on stairs (sec)	7.4 ± 0.5	7.6 ± 0.4	9.9 ± 1.1	12.3 ± 4.9	<0.03
Handgrip strength (kg)	26.1 ± 1.0	26.2 ± 1.0	23.3 ± 2.2	25.3 ± 3.2	
Fatigue visual analog scale (units, 0–10)	4.6 ± 0.2	4.4 ± 0.2	3.5 ± 0.6	4.9 ± 0.6	

* gr 3 *versus* gr 4.
† gr 1 *versus* gr 3.
CAD, catheter àdemeure.

DISCUSSION

This study has evaluated the potential benefits of complete intravenous nutrition given from the first postoperative day and until the patient was able to support himself or herself by spontaneous oral intake as judged by the clinician in charge. The nutritional support was prescribed individually to all patients according to daily measurements of energy expenditure and total nitrogen output. The therapeutical goal was to keep all TPN-treated patients close to nitrogen balance and in a positive energy balance (+20%) with basal ion, trace elements, and vitamin requirements supplied on a daily basis according to general recommendations. All pa-

Table 7. OUTCOME VARIABLES (days) AT THE END OF THE STUDY PERIOD AND ADDITIONAL MEDICAL TREATMENTS DURING THE STUDY PERIOD: ACTUAL TREATMENT

	Total Parenteral Nutrition gr 1	Glucose gr 2	gr 3	gr 4	ANOVA p
Hospital stay (days)	23.4 ± 1.4	24.5 ± 1.6	36.3 ± 3.9*	39.3 ± 5.3	<0.0001
Theoretical hospital stay (days)	17.3 ± 0.9	16.2 ± 0.9	20.6 ± 4.1	40.0 ± 8.3†	<0.0001
IV line	8.8 ± 0.5	7.7 ± 0.3	20.1 ± 3.7*	23.6 ± 3.9	<0.0001
Intensive care unit treatment	4.1 ± 0.4	3.5 ± 0.3	10.2 ± 3.5*	13.1 ± 2.2	<0.0001
Ventilator support	2.0 ± 0.3	2.2 ± 0.3	3.4 ± 1.1	10.8 ± 2.4†	<0.0001
O_2 support	3.4 ± 0.4	2.4 ± 0.2	5.9 ± 1.2*	8.5 ± 1.8†	<0.0001
Abnormal blood gas values	3.7 ± 0.4	2.9 ± 0.3	6.1 ± 1.3*	7.7 ± 2.9	<0.0001
Insulin (IE)	180 ± 47	88 ± 28	345 ± 215*	372 ± 90	<0.008
Antibiotics (days)	11.7 ± 0.8	10.7 ± 0.7	22.8 ± 3.3*	23.4 ± 4.1	<0.0001
Dextran colloid (mL)	1315 ± 149	1280 ± 72	2429 ± 536*	2805 ± 537	<0.0001
Albumin (mg)	504 ± 91	296 ± 50	445 ± 163	682 ± 171	
Plasma (mL)	1240 ± 186	2069 ± 520	4294 ± 1292*	5871 ± 1372	<0.0001
Blood (mL)	1003 ± 134	1261 ± 247	3357 ± 1585*	4203 ± 1069	<0.0001
Crystalline sol (mL)	25162 ± 2016	19080 ± 900	54793 ± 9980	73688 ± 11927	<0.0001

* gr 1 *versus* gr 3.
† gr 3 *versus* gr 4.
IE, international units.

Table 8. NUMBER AND RELATIVE RATE (in parentheses) OF SEVERE COMPLICATIONS DURING THE TOTAL HOSPITAL STAY IN THE VARIOUS GROUPS: ACTUAL TREATMENT

	Total Parenteral Nutrition (gr 1) (122)	Glucose (gr 2) (126)	gr 3 (24)	gr 4 (28)	Chi Square p
Mortality	2 (2)	6 (5)*	4 (21)	10 (36)†	<0.0001
Complications					
Myocardial infarction	2 (2)	2 (2)	2 (11)‡	3 (8)	<0.02
Myocardial insufficiency	10 (8)	13 (10)	4 (21)§	12 (43)‖	<0.0001
Myocardial arrythmia	11 (9)	10 (9)	5 (21)	7 (25)	<0.03
Thrombosis	2 (2)	4 (3)	4 (16)‡	3 (11)	<0.004
Suture insufficiency	3 (2)	5 (4)	2 (11)§	1 (4)	
Wound rupture	4 (4)	4 (4)	4 (16)‡	1 (4)	<0.03
Wound infection	14 (11)	11 (9)	4 (16)	3 (14)	
Pneumonia	12 (10)	9 (7)	1 (5)	3 (11)	
Atelectasis	18 (15)	12 (10)	4 (16)	11 (39)‖	<0.001
Urinary tract infection	12 (10)	6 (5)	2 (11)	6 (21)	<0.04
Sepsis	29 (24)	13 (11)	11 (53)†	12 (43)	<0.0001
Phlebitis	3 (2)	2 (2)	0	0	
Central venous line complications	7 (6)	5 (5)	4 (16)	5 (18)	<0.02
Central nervous system dysfunction¶	18 (15)	19 (16)	9 (37)‡	15 (54)‖	<0.0001

* $p < 0.15$ gr 2 *versus* gr 1.
† $p < 0.10$ gr 4 *versus* gr 3.
‡ $p < 0.05$ gr 3 *versus* gr 1.
§ $p < 0.10$ gr 3 *versus* gr 1.
‖ $p < 0.05$ gr 4 *versus* gr 3.
¶ Stroke or confusion.

tients scheduled for major surgery were qualified according to the protocol irrespective of being malnourished or not. Selections in any respect have not been done. No important differences appeared in results when patients were stratified for various degree of malnutrition before statistical computation. The results are presented strictly according to the protocol. Approximately 85% to 90% of all patients operated on in our hospital with the diagnoses according to the protocol have been included in the study over a 3-year period. The missing 10% to 15% were due to insufficient team and staff capacity. In such situations, exclusion of eligible patients were done by chance.

Table 9. NUMBER OF PATIENTS LEAVING THE HOSPITAL FOR HOME CONVALESCENCE OR CONTINUOUS INSTITUTIONAL CARE, AND THE TRANSPORTATION NEEDS FOR THOSE PATIENTS FROM THE HOSPITAL: ACTUAL TREATMENT

	Total Parenteral Nutrition gr 1 (121)	Glucose gr 2 (118)	gr 3 (21)	gr 4 (18)	Probability gr 1–4
Leaving hospital for home	88	78	11	10	
Leaving for institutional care	33	40	10	8	= 0.17
Leaving by own car or taxi	97	84	13	11	
Leaving by ambulance	24	34	8	7	= 0.10

The results in the current study cannot confirm general benefits of early and systematic postoperative nutrition to unselected patients, evaluated in terms of body composition, physiologic and functional patient criteria, hospital stay, the need of additional medical support treatment, serious complications, and mortality rate. This outfall may seem unexpected in the light of the well-documented relationship between undernutrition and worse outcome in noninterventional studies,[4,8,14,15] but agrees with recent controlled interventional studies.[16,17] Our results may also seem illogical because healthy individuals need good nutrition to remain in perfect shape and normal homeostasis.[1,18] Therefore, this should be true also for patients subjected to challenging operations. In approximately 20% of unselected patients undergoing major surgery, however, the omission of TPN was associated with increased morbidity and

mortality rates, although this phenomenon also may relate to the underlying disease. In these patients (group 3), however, TPN had a potential role as a life-supporting therapy, because they were unable to start oral support within 15 days after operation. The main explanation for the lack of benefits of early and systematic TPN when analyzed according to intent to treat was probably the fact that most (60%) of all our patients were able to eat freely within 8 to 9 days even after major surgical procedures, irrespective of being malnourished or not. This is obviously a too short time period for negative energy and nitrogen balance to be translated into significant limiting factors for healing and recovery in most patients. A factor contributing to this situation may be that glucose-treated patients started to adapt early to starvation by lowering energy expenditure, pulse rate, and body temperature (Table 5). In addition, an obligatory circulatory support by blood, albumin, and plasma certainly provides nitrogen reutilized for protein synthesis in purely glucose-treated patients, a fact that limits the possibility to compare strictly glucose *versus* TPN treatment.[13] This may explain why the glucose regimen was not hampered by a larger functional and nutritional deficit than was actually experienced. Forty per cent of all our patients experienced a complicated postoperative course (group 3 and 4) where suboptimal nutrition may has been a limiting factor or may even has been detrimental for outcome.

Early during this study it was recognized that some patients randomized to TPN did not tolerate their prescriptions according to the protocol. Therefore, it was decided to treat these patients with continuous TPN according to the randomization, but with daily modifications judged necessary on clinical grounds by the investigators (group 4). After analyses of the patient material, it is quite clear that this patient group experienced several complications including an extremely high mortality rate (36%). These patients had the same mean age as found in the other groups and they were recruited from all subgroups of diagnoses. Before operation, they did not have any larger frequencies of liver or kidney dysfunctions and they were not more malnourished than patients in the other subgroups. Evaluation of their records, however, suggest that the predominant postoperative problems were associated with cardiopulmonary complications. They were in the need of longer ventilatory support and needed more extra oxygen; they had higher pulse rate and a significantly higher frequency of myocardial insufficiency and atelectasis compared with patients on prolonged-glucose treatment (Table 5, 7, 8). Therefore, we conclude that this study has demonstrated that a substantial number of unselected surgical patients ($\approx$20%), so far with unclear preoperative predictive factors, do not tolerate the metabolic and fluid burden, which are associated with conventional and standard intravenous feeding. It is possible that this subgroup represents patients with hypertension and cardiac risk factors and thus contributes to attenuate various direct nutrition-related benefits of TPN when analyzed on overall patient materials.

The statistical outfall of complication and mortality rates by contingency table chi square analysis also showed a significantly higher mortality ($p < 0.006$) in group 3 (glucose to TPN) compared with patients treated with either TPN (group 1) or short-term glucose (group 2). Although it is possible that these patients (group 3) had some or similar complicating factors as group 4, it is also possible that poor nutrition during the initial 14 days contributed to the remarkably high mortality and complication rates in group 3, although it was not possible to prove this by the current number of patients in the subgroups. This suggestion may have support in a threefold higher mortality rate in glucose-treated patients (group 2) compared with TPN-treated patients (group 1), although not statistically significant ($p < 0.15$). The suspicion that undernutrition was a significant factor behind poor outcome in group 3 has support also in the findings of a trend to significantly more nutrition-related complications in group 3 than in group 4, such as wound rupture and suture insufficiency, which are usually not directly associated to cardiopulmonary problems. Therefore, this study supports but does not prove that prolonged use of only glucose/electrolytes after major surgery adds more serious complications, particularly with infectious and wound-healing character. This suggestion is also based on the findings that group 3 differed in several ways from TPN-treated patients in group 1, and in some aspects from TPN-treated patients in group 4, demonstrating a more pronounced repertoire of cardiopulmonary complications and worse function compared with group 3 (Table 6). It cannot be excluded, however, that heart-associated complications in semistarved patients in group 3 may be different in its nature than in patients belonging to group 4, although they were initially recruited from the same population.

We have reported that undernutrition is associated with profound biochemical alterations in the myocardium.[19–21] Such changes are probably developed to counteract the loss of contractile mass and thereby a lowering in cardiac output along with the loss of lean tissues. These cardiac alterations may create a sensitive and vulnerable physiologic state in the heart during stress and continuous semistarvation.[22–25] Therefore, two different regimens such as pure glucose treatment and TPN may induce seemingly similar heart complications evaluated from clinical symptoms, but with different basic mechanisms. Starvation may decrease the amount of contractile mass and thereby secondarily increase the excitability in the heart, whereas nutrition-induced stress may elicit infarction or heart failure simply by means of meta-

bolic and fluid overloads. This may be demonstrated by the fact that all TPN-treated patients (group 1, group 4) had similarly and significantly higher resting pulse rates than glucose-treated patients (group 2, group 3) In the evaluation of the cardiac complications, however, it is not possible to do any other classification than "yes or no" with regard to our patient material. A surprising finding in this study that standard supply of non-protein energy to cover 120% of the energy need resulted in glucosuria in most patients without any history of diabetes. This fact necessitates reevaluation of the optimal support with nonprotein energy to postoperative patients.

In conclusion, this study has demonstrated that suboptimal nutrition is not a limiting factor for outcome in most (60%) unselected patients undergoing major surgery. In the remaining patients (40%), however, there was evidence to support, based on statistically significant observations, that mortality rate, myocardial infarction, cardiopulmonary insufficiency, infectious related complications (sepsis, poor wound healing), and episodes of cerebral dysfunctions are increased when suboptimal nutrition is given in the postoperative period. In these patients, suboptimal nutrition includes both too much and too little nutrition. Future research should now focus on the possibilities to identify before operation those high-risk patients who will not tolerate standard nutrition after major surgery with a remarkable high mortality rate as a possible consequence and in those patients being unable to eat within 9 days after operation. Based on the current results and overall statistics according to actual treatment, we propose that prolonged postoperative glucose treatment beyond 9 to 14 days is associated with increased morbidity and mortality rates.

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