PERIOPERATIVE NUTRITIONAL SUPPORT IN PATIENTS UNDERGOING HEPATECTOMY FOR HEPATOCELLULAR CARCINOMA

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Abstract *Background.* Resection of hepatocellular carcinoma is associated with high rates of morbidity and mortality. Since intensive nutritional support can reduce the catabolic response and improve protein synthesis and liver regeneration, we performed a prospective study to investigate whether perioperative nutritional support could improve outcome in patients undergoing hepatectomy for hepatocellular carcinoma.

Methods. We studied 124 patients undergoing resection of hepatocellular carcinoma. Sixty-four patients (39 with cirrhosis, 18 with chronic active hepatitis, and 7 with no associated liver disease) were randomly assigned to receive perioperative intravenous nutritional support in addition to their oral diet, and 60 patients (33 with cirrhosis, 12 with chronic active hepatitis, and 15 with no associated liver disease) were randomly assigned to a control group. The perioperative nutritional therapy consisted of a solution enriched with 35 percent branched-chain amino acids, dextrose, and lipid emulsion (50 percent medium-chain triglycerides) given intravenously for 14 days perioperatively.

Results. There was a reduction in the overall postoperative morbidity rate in the perioperative-nutrition group as compared with the control group (34 percent vs. 55 percent; relative risk, 0.66; 95 percent confidence interval, 0.45 to 0.96), predominantly because of fewer septic complications (17 percent vs. 37 percent; relative risk, 0.57; 95 percent confidence interval, 0.34 to 0.96). There were also a reduction in the requirement for diuretic agents to control ascites (25 percent vs. 50 percent; relative risk, 0.57; 95 percent confidence interval, 0.37 to 0.87), less weight loss after hepatectomy (median loss, 0 kg vs. 1.4 kg; P = 0.01), and less deterioration of liver function as measured by the change in the rate of clearance of indocyanine green (−2.8 percent vs. −4.8 percent at 20 minutes, P = 0.05). These benefits were seen predominantly in the patients with underlying cirrhosis who underwent major hepatectomy. There were five deaths during hospitalization in the perioperative-nutrition group, and nine in the control group (P not significant).

Conclusions. Perioperative nutritional support can reduce complications after major hepatectomy for hepatocellular carcinoma associated with cirrhosis. (N Engl J Med 1994;331:1547-52.)

RESECTION of hepatocellular carcinoma is associated with high rates of morbidity and mortality.[1-3] This is because the majority of patients have cirrhosis, and hepatectomy causes further deterioration of liver function[4] due to the loss of functioning liver mass. Postoperative sepsis is the other main cause of morbidity and mortality and may be due in part to an enhanced catabolic response to surgery, increased proteolysis, and decreased immunocompetence in patients with cirrhosis who are already hypercatabolic,[5,6] malnourished, and immunocompromised.[7] Since intensive nutritional therapy can reduce the net catabolic response to surgery,[8] improve protein synthesis (which is critical for maintaining muscular, respiratory, metabolic, and immunologic function), and promote liver regeneration,[9,10] we performed a prospective study to investigate whether perioperative nutritional support could reduce postoperative morbidity and mortality in patients undergoing hepatectomy for hepatocellular carcinoma.

Methods

Randomization

From September 1990 through June 1993, 150 consecutive patients whose hepatocellular carcinoma was considered to be resectable on the basis of radiologic studies and hepatic-function tests were randomly assigned to receive either perioperative intravenous nutritional support in addition to their usual oral diet (the perioperative-nutrition group, 75 patients) or no additional therapy (the control group, 75 patients). The principal hepatic-function test used in this study was the indocyanine green clearance test. Indocyanine green is a dye that is rapidly eliminated by a normal liver after intravenous administration. It can be used as a sensitive and dynamic measurement of liver function.[11] Retention of more than 10 percent of the administered dose of indocyanine green 15 minutes after intravenous injection is an indication of reduced hepatic functional reserve and has been considered by some surgeons to be a contraindication to major hepatectomy.[12] However, in this study we included such patients as surgical candidates.

Sixty-four patients in the perioperative-nutrition group and 60 patients in the control group underwent hepatectomy. The other patients did not undergo hepatectomy because metastatic lesions were discovered in the abdominal cavity. Only the patients undergoing hepatectomy were studied and their data analyzed. Major hepatectomy was defined as the resection of two or more liver segments. Minor hepatectomy was defined as the resection of only one segment. The study protocol was approved by the ethics committee of the University of Hong Kong. Informed consent was obtained from all the patients included in the study.

Treatment

All patients in the perioperative-nutrition group had Broviac catheters implanted in the superior vena cava by surgical cutdown of the external jugular vein for parenteral nutrition. The parenteral nutrition was given 12 hours a night for seven nights before hepatectomy and was continued around the clock for seven days immediately after hepatectomy. The nutritional therapy consisted of a solution enriched with 35 percent branched-chain amino acids, at a dosage of approximately 1.5 g of amino acid per kilogram of body weight per day, and dextrose and lipid emulsion (50 percent medium-chain triglycerides) providing 30 kcal per kilogram per day. Vitamins and trace minerals were added to the parenteral-nutrition fluid daily. The total volume of parenteral-nutrition fluid was limited to 1.75 liters per day.

The patients in the control group had their usual oral diet preoperatively. In the postoperative period, they received 5 percent dextrose and normal saline with a volume and sodium content approximately equal to those of the fluid given to the patients in the perioperative-nutrition group.

All the patients received 2 g of cefotaxime at the time of the induction of general anesthesia. Postoperatively, all patients re-

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ceived 2 g of cefotaxime intravenously every 12 hours for three days and 25 g of albumin intravenously daily for five days. They were encouraged to resume oral feeding as soon as bowel function returned. Fluid balance and body weights were measured daily to avoid fluid overload.

The surgical treatment was standardized. Hepatectomy was performed by two surgeons using the same technique — i.e., preliminary control of vascular inflow and outflow, followed by transection of the liver parenchyma. All resected specimens were examined histologically to determine the stage of the disease and to diagnose cirrhosis and chronic active hepatitis.

Assessment

Before randomization, three types of measurement were made. First, an anthropometric assessment included measurements of body weight, triceps skin-fold thickness, midarm circumference, and grip strength. Second, a liver biochemical assessment included measurements of serum bilirubin and liver enzymes; prothrombin time; serum concentrations of albumin, transferrin, prealbumin, and retinol-binding protein; plasma glucose; and indocyanine green clearance, which was expressed as the percentage of the dose that was retained in the blood 15 and 20 minutes after the intravenous administration of dye. Finally, an immunologic assessment included measurements of the response of lymphocytes to stimulation with phytohemagglutinin and serum immunoglobulin levels.

Serum bilirubin and liver enzymes were measured daily for eight days after hepatectomy. Serum concentrations of transferrin, prealbumin, and retinol-binding protein were measured on postoperative days 1, 4, 6, and 8. Anthropometric measurements, the indocyanine green clearance test, determinations of serum immunoglobulins, and tests of the lymphocyte response to phytohemagglutinin were repeated on postoperative day 8.

The assessment of outcome was based on mortality in the hospital, overall postoperative morbidity, changes in anthropometric measurements, and liver and immunologic function. Mortality in the hospital was defined as death during the hospital admission for surgery. Postoperative morbidity was determined by independent observers and defined as follows. Pulmonary infection was defined as the presence of pneumonic or atelectatic changes on radiographs associated with a positive sputum culture. Wound infection was defined as erythema and induration of a wound associated with purulent discharge that was positive on bacterial culture. A subphrenic abscess was defined as a collection of pus with or without necrotic material associated with a positive bacterial culture. Central-line sepsis was defined as a positive culture of the catheter tip in the presence of a febrile episode. Pleural effusion was considered a complication when the collection of fluid caused dyspnea and tapping was required for relief. Ascites was considered a complication when the accumulation was massive, leading to dyspnea or leakage through the abdominal wound, and a diuretic agent was needed for control. The diuretic agents were prescribed by medical staff members who were not involved in the study. Renal failure was defined as an elevation of the postoperative serum creatinine to more than two times the upper limit of normal.

Statistical Analysis

The overall rate of postoperative morbidity associated with hepatectomy for hepatocellular carcinoma was 47 percent in Hong Kong.[3] A reduction of the rate by half was considered necessary to indicate the efficacy of perioperative nutritional support. To detect a difference of this magnitude at a level of statistical significance of 0.05 and a power of 0.80, 60 patients were required in each group.[13]

The Mann–Whitney U test was used to compare continuous variables. The chi-square test (with Yates' correction if there were more than 10 cells) was used to compare discrete variables. All P values of 0.05 or less were considered to indicate statistical significance (by the two-tailed test). Calculations were made with SPSS computer software (SPSS, Chicago). The important end points are presented as relative risks and 95 percent confidence intervals, which were calculated with Epi Info 6 computer software (World Health Organization, Geneva).

Table 1. Preoperative Data on Patients Receiving Perioperative Nutrition and Control Patients.*

Variable	Perioperative Nutrition (N = 64)	Controls (N = 60)	Normal Reference Value
Age — yr	54 (28–72)	53 (33–79)	—
Sex — M/F	56/8	53/7	—
Body weight — kg	57 (41–94)	57 (44–82)	—
Weight loss — kg	2.05 (0–11.4)	1.85 (0–10)	—
Weight loss >10% — % of patients	18	14	—
Midarm circumference — cm	26 (19–32)	28 (20–74)	28†
Triceps skin-fold thickness — mm	10.6 (3.2–21)	12 (4–42)	15†
Grip strength — kg	27 (4–50)	28 (5.1–47)	30†
Serum determinations			
Albumin — g/liter	42 (31–51)	43 (29–50)	45‡
Transferrin — mg/liter	2525 (423–3800)	2238 (982–4150)	2000§
Prealbumin — mg/liter	183 (42.3–438)	160 (39–340)	200§
Retinol-binding protein — mg/liter	26 (15–63)	23 (15–65)	40§
Retention of indocyanine green — %			
At 15 min	12.4 (2.7–50)	10.2 (4.2–39.2)	7.0¶
At 20 min	6.8 (1–39)	5.3 (1.6–29)	3.1¶
Serum immunoglobulins — mg/dl			
IgG	1500 (926–2850)	1378 (682–2708)	540–1663‖
IgA	320 (144–680)	280 (79–794)	66–344‖
IgM	134 (36–390)	124 (47–352)	39–290‖
Stimulation index**	35 (4.5–302)	29 (2–162)	67.7 (20–187)††

*Values followed by values in parentheses are medians and ranges.

†Median value in local population (unpublished data).

‡Lower limit in local population (unpublished data).

§Lower limit according to Buzby and Mullen.[14]

¶According to Caesar et al.[11]

‖According to Ward and Randall.[15]

**Calculated as the mean count of lymphocytes per minute in a sample stimulated with 1 percent phytohemagglutinin divided by the mean count per minute in an unstimulated sample.

††According to Fan et al.[16]

Results

The two groups of patients were similar in terms of age, sex, the amount of weight lost, the results of the preoperative assessment (Table 1), the incidence of underlying cirrhosis, the stage[17] of disease according to the tumor–node–metastasis (TNM) classification system, and the proportion of patients undergoing major hepatectomy (Table 2). There were more patients in the perioperative-nutrition group who retained more than 10 percent of the dose of indocyanine green at 15 minutes than in the control group (67 percent vs. 47 percent, P = 0.03). Among the patients undergoing major hepatectomy, the proportion who retained more than 10 percent of the dose at 15 minutes was also higher in the perioperative-nutrition group (64 percent vs. 43 percent, P = 0.048).

Table 2. Intraoperative Data on Patients Receiving Perioperative Nutrition and Control Patients.

Variable	Perioperative Nutrition (N = 64)	Controls (N = 60)
Nontumorous liver specimens — no. of patients (%)		
Cirrhosis	39 (61)	33 (55)
Chronic active hepatitis	18 (28)	12 (20)
Normal	7 (11)	15 (25)
Tumor size — cm		
Median	9.3	9.0
Range	2–18	0.5–25
Major hepatectomy — no. of patients	47	42
Right hepatic lobectomy	28	20
Right extended lobectomy	10	11
Left hepatic lobectomy	2	5
Right trisegmentectomy	4	3
Left extended lobectomy	3	3
Minor hepatectomy — no. of patients	17	18
Left lateral segmentectomy	8	2
Subsegmentectomy	9	16
Intraoperative blood loss — liters		
Median	2.6	1.9
Range	0.3–20	0.4–10.5
TNM stage — no. of patients*		
I	2	3
II	21	20
III	30	26
VI A	10	10
VI B	1	1

*According to the Liver Cancer Study Group of Japan.[17]

Overall, 22 of 64 patients in the perioperative-nutrition group (34 percent) had postoperative morbidity, as compared with 33 of 60 patients in the control group (55 percent; relative risk, 0.66; 95 percent confidence interval, 0.45 to 0.96) (Table 3). The difference was mainly due to a reduction in the incidence of septic complications in the perioperative-nutrition group (11 patients [17 percent] vs. 22 patients [37 percent]; relative risk, 0.57; 95 percent confidence interval, 0.34 to 0.96). The need for diuretic therapy to control ascites was significantly lower in the perioperative-nutrition group than in the control group (16 patients [25 percent] vs. 30 patients [50 percent]; relative risk, 0.57; 95 percent confidence interval, 0.37 to 0.87). Hospital mortality was 8 percent in the perioperative-nutrition group and 15 percent in the control group (P = 0.30).

In the postoperative period, there was no significant difference between the two groups in prothrombin time, serum bilirubin measurements, or liver-enzyme levels, except for serum aspartate aminotransferase (Table 4). Plasma glucose, serum urea, serum transferrin, serum prealbumin, and serum retinol-binding protein levels were significantly higher in the perioperative-nutrition group than in the control group on most of the postoperative days (Table 4).

On postoperative day 8, the anthropometric measurements were similar in the two groups (Table 5). However, a comparison of weight loss after hepatectomy (measured as the preoperative value minus the postoperative value for individual patients) indicated that the patients in the perioperative-nutrition group lost less weight (median, 0 kg; range, −6.5 to 10) than the patients in the control group (median, 1.4 kg; range, −1.7 to 7.0; P =0.01).

Nearly all the patients had a deterioration in indocyanine green clearance after hepatectomy, but the patients in the perioperative-nutrition group had less deterioration than the control patients. The median change in indocyanine green retention at 15 minutes (measured as the preoperative value minus the postoperative value for individual patients) was −4.4 percent (range, 8.0 to −50.8) in the perioperative-nutrition group and −7.2 percent (range, 15.8 to −44.8) in the control group (P = 0.07). The median change in indocyanine green retention at 20 minutes was −2.8 percent (range, 7.3 to −50.5) in the perioperative-nutrition group and −4.8 percent (range, 9.9 to −44.3) in the control group (P = 0.05). Measurements of serum immunoglobulins and of the lymphocyte response to stimulation with phytohemagglutinin on postoperative day 8 revealed no significant difference between the two groups (Table 5).

The data were further analyzed to determine whether patients with underlying chronic liver disease benefited more from perioperative nutritional support than patients with normal livers. Patients with cirrhosis who received perioperative nutritional support had better outcomes than control patients with cirrhosis in that the overall rate of postoperative morbidity and the need for diuretic therapy to control ascites were reduced and weight loss was also less severe (Table 6). Patients with no associated liver disease who received perioperative nutritional support had a lower overall rate of postoperative morbidity

Table 3. Overall Postoperative Morbidity and Hospital Mortality.*

Variable	Perioperative Nutrition (N = 64)	Controls (N = 60)
Septic complications†		
Pulmonary infection	5 (1)	15
Wound infection	3	5
Subphrenic abscess	4	5 (4)
Urinary tract infection	0	2
Infected ascites	1	2
Biliary fistula	4	5
Central-catheter sepsis	1	0
Other complications		
Wound dehiscence	1	1
Myocardial infarction	0	3 (1)
Intraabdominal bleeding	4	1
Variceal bleeding	1	0
Peptic ulcer bleeding	1	2
Intestinal obstruction	1	0
Pleural effusion	9	12
Hepatic coma	4 (4)	4 (4)
Renal failure	2	1
Ascites requiring diuretic agent for control‡	16	30
Hospital mortality	5	9

*Some patients had more than one type of postoperative morbidity. Overall, postoperative morbidity occurred in 22 patients in the perioperative-nutrition group and 33 patients in the control group (34 percent vs. 55 percent, chi-square = 5.29, P = 0.02). Parentheses indicate the number of patients who died from the complication in the group shown.

†Septic complications occurred in 11 patients in the perioperative-nutrition group and 22 patients in the control group (17 percent vs. 37 percent, chi-square = 5.97, P = 0.01).

‡Ascites requiring the use of diuretic agents occurred in 25 percent of the perioperative-nutrition group and 50 percent of the control group (chi-square = 8.23, P = 0.004).

Table 4. Postoperative Serum Biochemical Data on Patients Receiving Perioperative Nutrition and Control Patients.

Variable*	Perioperative Nutrition (N = 64)	Controls (N = 60)	P Value†
	median (range)		
Aspartate aminotransferase (units/liter)			
Day 1	233 (16–2340)	226 (20–1860)	0.97
Day 2	169 (33–1690)	151 (17–1360)	0.11
Day 3	89 (40–538)	80 (20–620)	0.087
Day 4	66 (31–196)	53 (18–394)	<0.006
Day 5	54 (27–288)	42 (25–341)	<0.002
Day 6	52 (28–216)	39 (22–291)	<0.001
Day 7	51 (26–202)	40 (22–237)	<0.001
Day 8	59 (29–220)	43 (21–179)	<0.001
Glucose (mg/dl)			
Day 1	144 (83–281)	133 (85–247)	0.32
Day 2	144 (79–333)	126 (5–317)	0.001
Day 3	142 (85–405)	122 (72–257)	<0.001
Day 4	142 (52–533)	115 (20–284)	<0.001
Day 5	132 (45–779)	118.8 (58–236)	0.013
Day 6	133 (47–416)	131.4 (76–297)	0.85
Day 7	139 (67–405)	129.6 (92–297)	0.13
Day 8	117 (56–412)	109.8 (74–320)	0.45
Urea (mg/dl)			
Day 1	27.3 (8.4–59.4)	23.4 (9.0–63.6)	0.56
Day 2	27.6 (14.4–55.2)	21.6 (7.8–88.8)	<0.002
Day 3	31.8 (9–75.6)	22.2 (7.8–89.4)	<0.001
Day 4	36.6 (13.2–92.4)	21.9 (5.4–69.0)	<0.001
Day 5	34.2 (16.2–101.4)	23.4 (6.6–70.8)	<0.001
Day 6	33.6 (19.8–106.8)	24.6 (7.8–63.0)	<0.001
Day 7	36.3 (16.8–128.4)	24.0 (6.6–61.8)	<0.001
Day 8	36.3 (19.8–184.2)	26.4 (7.2–68.4)	<0.001
Transferrin (mg/liter)			
Day 1	1575 (763–3150)	1575 (763–3149)	0.68
Day 4	1298 (495–2950)	1175 (631–2700)	0.24
Day 6	1362 (598–2460)	1175 (220–2825)	0.013
Day 8	1465 (700–2700)	1153 (514–3000)	0.013
Prealbumin (mg/liter)			
Day 1	150 (94–295)	128 (59–293)	0.017
Day 4	106 (65–173)	83 (24–188)	0.001
Day 6	110 (53–710)	85 (20–213)	0.001
Day 8	111 (45–403)	87 (33–291)	<0.002
Retinol-binding protein (mg/liter)			
Day 1	10 (0–54.7)	8 (0–32.3)	0.103
Day 4	9.1 (1.7–38.3)	5.6 (0–21.7)	<0.001
Day 6	11 (3–44)	7.3 (0–23.5)	<0.001
Day 8	12.7 (1–44.8)	9 (0–30.7)	<0.001

*To convert values for glucose to millimoles per liter, multiply by 0.056; to convert values for urea to millimoles per liter, multiply by 0.36.

†By the Mann–Whitney U test.

than control patients, but the other benefits were not obvious.

Further analyses were performed to determine how the extent of hepatectomy influenced the outcome. Patients who underwent major hepatectomy had a lower overall rate of postoperative morbidity, less deterioration in the clearance of indocyanine green, a reduced need for diuretics, and less weight loss after hepatectomy (Table 6). These benefits were not seen in patients who underwent minor hepatectomy. An additional analysis of the influence of the extent of hepatectomy in the patients with cirrhosis demonstrated only that patients with cirrhosis who underwent major hepatectomy benefited from perioperative nutritional support; those who underwent minor hepatectomy did not (Table 6).

Two patients had preoperative complications related to nutritional therapy (one had catheter sepsis and the other a badly positioned catheter), and two had postoperative complications (hyperglycemia and diuresis in the absence of a history of diabetes mellitus). None of the patients died for reasons related to nutritional support.

Discussion

Modern surgical techniques have reduced the operative morbidity and mortality associated with the resection of hepatocellular carcinoma, but only in patients without underlying liver disease[18,19] and those with cirrhosis undergoing minor hepatectomy for small tumors.[20] When major hepatectomy was carried out in patients with underlying cirrhosis, the operative mortality ranged from 26 to 50 percent.[18,19,21,22] Major hepatectomy has therefore been considered to be contraindicated[23,24] in patients with cirrhosis, especially if they retained more than 10 percent of a dose of indocyanine green 15 minutes after intravenous administration.[12] In Hong Kong, many patients with hepatocellular carcinoma present with large tumors associated with cirrhosis, and there is a policy of performing major hepatectomy in these patients. We have shown that perioperative nutritional support offers a benefit in terms of better protein synthesis, preserved liver function, and reduced morbidity. The benefit was most evident in patients undergoing major hepatectomy, even though the proportion who retained more than 10 percent of the dose of indocyanine green at 15 minutes was higher than that in the control group.

Perioperative nutritional support has been shown to be useful in reducing the rate of postoperative complications in severely malnourished patients.[25] In our study, the incidence of malnutrition (defined as the loss of more than 10 percent of usual body weight[26]) was 15 percent, indicating that many patients with normal nutritional status were included. This is because many patients with hepatocellular carcinoma do not lose substantial amounts of weight at the stage when their tumors are resectable. Moreover, hepatectomy is a major operation that induces a severe catabolic response, even in patients with normal nutritional status. Therefore, the degree of malnutrition was not an important consideration in the criteria for inclusion. Since many of our patients were not cachectic, preoperative nutritional support was given at night to allow patients to be fully ambulatory during the day and to compensate for the lack of nutritional intake when they underwent preoperative investigation.

A solution enriched with branched-chain amino acids was chosen for this study because it is anticatabolic,[27] promotes hepatic, muscle, and plasma protein synthesis in patients with chronic liver diseases,[28,29] and accelerates liver regeneration in animals.[30] Since patients with cirrhosis often have glucose intolerance and insulin resistance,[31] branched-chain amino acids may also be useful in providing energy to the liver and peripheral tissues,[32] especially in the immediate postoperative period, when liver function is abnormal and oral intake is lacking.

To avert glucose intolerance, a lipid emulsion was included in the regimen. However, the usual prepara-

Table 5. Postoperative Data on Patients Receiving Perioperative Nutrition and Control Patients.*

Variable	Perioperative Nutrition (N = 64)	Controls (N = 60)
	median (range)	
Body weight — kg	55 (26–76)	55 (38–82)
Midarm circumference — cm	26 (10–31)	26 (20–78)
Triceps skin-fold thickness — mm	11.2 (3.7–20)	10.5 (4–27)
Grip strength — kg	23 (5–45)	25 (10–44)
Retention of indocyanine green — %		
At 15 min	15.2 (5.4–66.5)	18.1 (3.3–67)
At 20 min	8.7 (2.0–59.3)	10.9 (1.3–58.5)
Serum immunoglobulins — mg/dl		
IgG	1415 (866–3060)	1259 (812–2414)
IgA	331 (156–792)	287 (142–564)
IgM	162 (28–446)	145 (54–386)
Stimulation index†	12.0 (2.1–199)	18.8 (3.8–89)
Hospital stay — days	14.5 (8–51)	16 (2–126)

*None of the differences between groups were statistically significant.

†Calculated as the mean count of lymphocytes per minute in a sample stimulated with 1 percent phytohemagglutinin divided by the mean count per minute in an unstimulated sample.

tion of lipid emulsion consists of long-chain triglycerides, which are considered inadvisable for patients with cirrhosis who have impaired synthesis of apoprotein C-II,[33] albumin, hepatic triglyceride lipase,[34] and carnitine.[35] Medium-chain triglycerides, which have a reduced dependence on albumin and apoprotein C-II for breakdown[36] and on carnitine for intracellular metabolism,[37] were therefore included. An additional advantage of medium-chain triglycerides is that they are readily oxidized by all body tissues and little is deposited in the liver.[37] We also demonstrated previously that the mixture of long-chain and medium-chain triglycerides could be rapidly eliminated from the blood in patients with cirrhosis.[38]

There have been few reports of perioperative nutritional support for patients undergoing hepatectomy. Reilly et al.[39] showed that postoperative nutritional therapy could improve muscle function in patients undergoing liver transplantation, allowing early weaning from respirators. However, Kanematsu et al.[40] showed that the postoperative administration of a solution enriched with branched-chain amino acids did not reduce the incidence of hepatic coma. In that study, the possible benefits of such a solution on nutritional variables were not evaluated. In the present study, we demonstrated that perioperative nutritional support could lead to less weight loss and to higher serum concentrations of proteins with a short half-life as well as to higher concentrations of glucose and urea. The patients' skin-fold thickness, midarm circumference, and grip strength were not altered by the nutritional support. Probably these measurements were insensitive to short-term changes. Like Kanematsu et al.,[40] we found the incidence of fatal hepatic coma to be the same between the two groups of patients. We identified the cause of hepatic coma as an error in surgical technique that led to massive hemorrhage. In this situation, hepatic coma progressed rapidly and was not reversed by nutritional support.

The reduction in postoperative morbidity in this study did not shorten the hospital stay. Although there was a significant difference between study groups in the incidence of septic complications, there was no major difference in postoperative immunologic measures. The majority of the septic complications were due to pulmonary infection.

In conclusion, perioperative nutritional support in the form of a solution enriched with branched-chain amino acids, dextrose, and medium-chain triglycerides is beneficial in reducing postoperative morbidity. It is indicated in patients undergoing major hepatectomy, especially when the liver is cirrhotic.

Table 6. Comparison of Outcomes between Subgroups According to Histologic Features of Uninvolved Liver and Extent of Hepatectomy.

Variable	No. of Patients	Overall Postoperative Morbidity	P Value	Change in 20-Min Indocyanine Green Retention (%)	P Value	Need for Diuretic Agents	P Value	Body Weight Lost (kg)	P Value	Mortality
		%		median (range)		%		median (range)		%
Cirrhosis										
Nutrition	39	31	0.01	−3.3 (7.3 to −50.5)	NS	28	0.006	0 (−6.5 to 12.5)	0.006	8
Control	33	61		−4.5 (4 to −29)		71		1.45 (−1.7 to 6.6)		15
Chronic active hepatitis										
Nutrition	18	50	NS	−2 (4.1 to −27.9)	NS	18	NS	0.3 (−3.1 to 3)	NS	5
Control	12	25		−14.2 (9.9 to −44.3)		42		2.25 (0 to 7)		25
Normal liver										
Nutrition	7	14	0.045	−2.0 (1.9 to −41.7)	NS	29	NS	−0.3 (−3.5 to 0.8)	NS	14
Control	15	60		−4.9 (2.4 to −36.3)		36		1.0 (−4 to 4)		6.7
Major hepatectomy										
Nutrition	47	36	0.03	−3.2 (4.1 to −50.5)	0.05	20	0.002	0.3 (−6.5 to 12.5)	0.002	11
Control	42	60		−6.2 (2.4 to −44.3)		59		1.65 (−4 to 7)		17
Minor hepatectomy										
Nutrition	17	29	NS	−0.4 (7.3 to −23.7)	NS	41	NS	−0.15 (−3.2 to 30)	NS	0
Control	18	44		−2.5 (9.9 to 17.5)		33		1.0 (−1.7 to 4)		11
Cirrhosis and major hepatectomy										
Nutrition	27	33	0.02	−3.6 (2.8 to −50.5)	NS	22	<0.001	0.5 (−6.5 to 12.5)	0.016	11
Control	21	67		−6.0 (2 to −29)		79		1.7 (−2 to 6.6)		14
Cirrhosis and minor hepatectomy										
Nutrition	12	25	NS	−0.75 (7.3 to −10)	NS	42	NS	−0.5 (−3.2 to 2.7)	NS	0
Control	12	50		−3.1 (4 to −17.5)		42		1.0 (−1.7 to 4)		16

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