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A Randomized Clinical Trial of Early Enteral Nutrition to Prevent Infectious Complications in Patients With Extensive Liver Resection

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After major liver resections, infections and liver insufficiency are the most common complications; these may coincide. We performed a randomized clinical trial to clarify ability of early enteral nutrition to prevent infectious complications and liver failure following major hepatectomy. We prospectively allocated consecutive patients who underwent major liver resection into either an early enteral nutrition group in which such nutrition was initiated on the first postoperative day or a nonenteral nutrition group. The primary study endpoint was rate of infectious complications. Thirty-two patients were randomly allocated to the enteral nutrition group, while 31 were assigned to the nonenteral nutrition group. No significant difference in rate of infection complications was evident between enteral (9.4%) and nonenteral group (22.6%, $P = 0.184$). However, complications of grade III severity or worse were significantly less frequent in the enteral (9.4%) than in the nonenteral group (32.3%, $P = 0.031$). Further, postoperative serum concentrations of pre-albumin and reduced-state albumin were greater in the enteral than in the nonenteral group. Early enteral nutrition did not significantly improve prevention of infectious complications, but some effectiveness in preventing severe complications and improving nutritional status was demonstrated.

Key words: Enteral nutrition – Surgical site infection – Remote infection – Liver surgery

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Safe removal of extensive liver tumor burden has been a main focus for hepatobiliary surgeons. While extensive hepatectomy often is necessary to curatively resect aggressive and advanced tumors in the liver, such major liver resections involve considerable reduction of hepatic mass, which can lead to clinical decompensation including sepsis and hepatic insufficiency.

Sepsis and transient liver insufficiency are the most common complications after liver resections,[1] often occurring together.[2] A well-known synergism between sepsis and liver dysfunction can contribute importantly to a poor outcome.[2,3] Especially in patients with poor liver function or an extensive hepatectomy, postoperative infection remains a major threat that can lead to liver failure and other fatal complications. Extent of liver resection was reported to influence overall incidence of complications after hepatectomy,[4] and a major hepatic resection was reported to predict hospital mortality.[5]

Most patients with elective liver resection need no special nutritional support because recovery usually is sufficiently smooth to permit initiation of oral intake within the first few days. Some patients, however, recover too slowly for timely, sufficient oral nourishment. Such patients often incur septic complications, and mortality may result. After major liver resection, nutritional state can support or inhibit liver regeneration. Urgently needed after such resections, regeneration requires appropriate metabolic substrates. In extreme instances, competition for substrates ensues between support of the acute-phase response, liver regeneration, and—if postoperative sepsis occurs—host defense.[6] Accordingly, appropriate nutritional support can be pivotal for liver regeneration and recovery for some patients following major hepatectomy.[7]

Early postoperative enteral nutrition has been reported to prevent infectious complications and decrease incidence of bowel obstruction after major visceral surgery.[8,9] Use of enteral nutrition is considered to enhance gut wall barrier function and modulate inflammatory responses, which ultimately could reduce risk of liver failure.

We therefore postulated that early enteral nutrition might be beneficial after extended liver resection by decreasing infectious complications, resulting in reduced risk of liver failure. The primary aim of the present study was to evaluate whether early enteral nutrition could help prevent infectious complications for patients with extensive liver resection.

Methods

Patients undergoing major resections for primary or secondary liver tumors or for noncancerous liver disease between October 2011 and December 2013 were recruited for the present single-center randomized controlled trial. Participating patients were randomized to either receive early postoperative enteral nutrition or not. The study protocol was approved by the Institutional Ethical Committee at Yokohama City University, Japan (notice of approval of IRB protocol number, B110901026). Written informed consent was obtained from all patients involved. The study was registered under UMIN reference number 000008628.

Exclusions and randomization

Exclusion criteria were hepatectomy including resection of the bile duct with reconstruction using a segment of intestine; resection of less than 3 segments of liver (minor liver resection); anticipated difficulty of intraoperative feeding tube insertion because of dense intraperitoneal adhesions from a previous operation; and an operation representing class III or greater according to US Centers for Disease Control and Prevention (CDC) guidelines.[10] All patients eligible for the study underwent percutaneous feeding tube insertion into jejunum during the resection operation. Patients were randomized to receive early postoperative enteral nutrition or not. Simple randomization was carried out.

Interventions during the study

Irrespective of study arm, all patients were given prophylactic antibiotics, specifically flomoxef sodium (Shionogi, Osaka, Japan). On the day of operation, 1 g was administered 30 minutes before surgery; 1 g every 3 hours during surgery; 1 g 2 hours after completion of surgery; subsequently, 1 g was given every 12 hours on postoperative days (POD) 2 to 4.[11]

During the hepatectomy procedure, parenchymal dissection was performed using the CUSA system (Valley, Boulder, Colorado). Salient monopolar instrumentation (Medtronic Advanced Energy, Portsmouth, New Hampshire) was used additionally for hemostasis in the transection plane. Intraoperative ultrasonography (US, SSD-2000 or ProSound SSD-4000, Aloka, Tokyo, Japan) was used to identify any tumors not detected preoperatively, and to confirm relationships between tumors and vasculobiliary structures. When necessary, the liver pedicle was clamped intermittently using Pringle's maneuver or selective clamping in cycles of 15 minutes of clamping and 5 minutes of reperfusion. The Brisbane 2000 terminology of the International Hepato-Pancreato-Biliary Association was used to designate operative procedures.[12] In this study, en masse removal at least 3 segments with or without some partial resections was defined as major hepatectomy, while resections involving less than 3 segments were defined as minor hepatectomy.

In both arms of the study, after removing resected liver and ensuring hemostasis, an 8 Fr feeding tube (Kangaroo ED Tube, Covidien, Dublin, Ireland) was inserted percutaneously into the jejunum, 30 to 40 cm distal to the ligament of Treitz. The tube was brought out through a separate stab wound in the left upper quadrant of the anterior abdominal wall. A closed-suction drain (J-Vac, Johnson & Johnson, Somerville, New Jersey) was placed near the transection plane of the liver parenchyma in all patients. Patient warming devices were used during the operation, and wound washout was performed using warm sterile saline after fascial closure and before skin closure.

Enteral nutrition and postoperative management

All patients followed the same postoperative care protocol with the exception of enteral nutrition. In the early enteral nutrition group, enteral feeding through the jejunostomy tube implanted during the operation was started immediately after recognition in abdominal radiographs obtained on the morning of POD 1 of contrast material passing into the right colon from the previous day's intraoperative cholangiogram. For patients whose contrast material had not reached the right colon that morning, enteral feeding still was started on POD 1, usually in the late afternoon. Enteral feeding was started as 1 kcal/mL given at a slow continuous rate, 10 mL/hour over 24 hours. The rate was increased (by 10 mL/h/d) until it reached 50 mL/h with care to avoid diarrhea and other complications. A commercially available elemental diet was given (Elental, Ajinomoto Pharma, Tokyo, Japan). All patients in both study arms began a light diet on day 1 or 2 and could progress to full meals if tolerated. Enteral nutrition was decreased in proportion to the increase in oral intake even if the rate of enteral feeding had not reached 50 mL/h.

Ordinarily, the abdominal drainage tube was removed on POD 2 to 4, immediately after the following criterion was met: a maximum daily value for the bilirubin concentration ratio (the ratio of bilirubin concentrations in drainage fluids to those in serum) times milliliters of drainage fluid below 200. Exceptions were made for development of intra-abdominal infection or bile leakage.[13] Patients were discharged from the hospital when these predetermined criteria had been met: no signs of systemic infection such as fever; meals tolerated without nausea or vomiting; normal liver function test values; and adequate pain control with oral analgesia.

Study endpoints

The primary endpoint of this study was the rate of infectious complications [either surgical site infection (SSI) or remote infection] at the 4-week follow-up assessment after treatment. SSIs were defined as incisional (either superficial or deep) infection or organ/space infection. Incisional infection was defined as cellulitis, induration, or purulent discharge at the closure site. Organ/space infection was defined as radiologic evidence of a fluid collection requiring drainage and or antibiotic therapy. Remote infection was defined as detection of bacteria in sputum, blood, or urine, accompanied by signs of inflammation such as fever.

All inpatient morbidity was recorded prospectively. Complications were defined as any deviation from an uneventful postoperative course. Assessment of complications followed a recently published standardized complication classification system (Clavien-Dindo classification).[14] Postoperative hemorrhage, bile leakage, and liver failure were defined and graded according to the International Study Group of Liver Surgery (ISGLS).[15–17] If deterioration occurred postoperatively, especially when liver failure was a possibility, enteral feeding could be carried out according to individual attending physicians. Secondary endpoints involved overall morbidity, hospital stay, rate of conversion to enteral nutrition, and clinical variables outlined below.

Other data recorded

Operative time was measured from skin incision to application of dressing. Investigators obtained a complete medical history, vital signs, and laboratory tests. Physical status (PS) was determined according to the American Society of Anesthesiologists (ASA) classification.[18] Nutritional status was evaluated by a prognostic nutritional index (PNI) based on peripheral blood lymphocyte count and serum

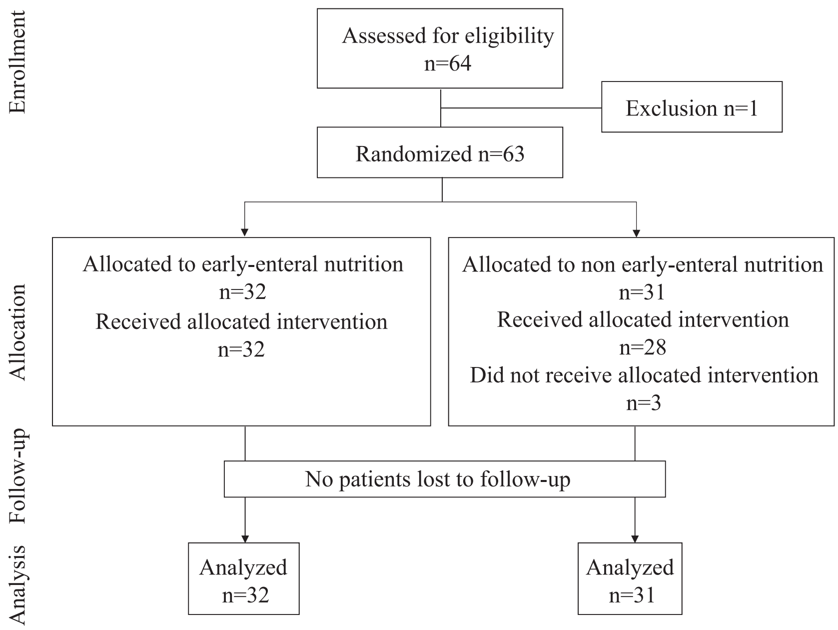

Fig. 1 CONSORT diagram showing the flow of participants through each stage of the trial.

albumin concentration,[19] which was calculated by the following formula: lymphocyte count (cells/mm^2) $\times$ 0.05 + serum albumin (g/dL) $\times$ 10. Vital signs were recorded daily while the patient was hospitalized and at the 4-week follow-up assessment. Hematologic and biochemical tests were performed before surgery, immediately after surgery, and at 1 and 2 weeks after surgery, including proteins with rapid turnover such as prealbumin and retinol-binding protein.

Serum albumin microheterogeneity also was measured. Oxidized albumin and reduced albumin were determined by high-performance liquid chromatography.[20] Oxidized albumin percentage was calculated using following formula: oxidized albumin/(oxidized albumin + reduced albumin) $\times$ 100.

Investigators performed detailed wound assessments at least every other day for up to 7 days during hospitalization, at discharge, and at the 4-week follow-up visit. When patients were randomized to the no early-enteral-nutrition group, the percutaneously-inserted tube was not used unless necessitated by a complication as judged by attending physicians.

Sample size

This is a randomized phase II study. We primarily aim to assess whether the incidence of SSI is less than the null proportion in each arm. Previously reported incidence of infectious complications after liver resection has been approximately around 20%.[21,22] In our study, we predicted a likely incidence of 5% in early-enteral-nutrition group. When the null proportion was set at 20% and the alternative proportion was set at 5%, a minimum of 28 patients were required in each group to achieve 80% power for a single arm test at a 1-sided significance level of 5%. We therefore aimed for 32 patients per group.

Statistical analysis

Continuous data are expressed as mean ($\pm$SD) or median (range), and were analyzed using the parametric Student's t test and the nonparametric Mann–Whitney U test respectively. The χ^2 test or Fisher's exact test was used for analysis of categoric variables. A difference was considered significant when the 2-sided P value was below 0.05.

Results

Number of entries

During the study period, 64 patients were eligible for entry. One patient whose feeding tube would have been difficult to insert intraoperatively because of severe intraperitoneal adhesion caused by a previous operation was excluded. Then 32 patients were randomized to the early enteral nutrition group, with 31 randomized to the nonenteral nutrition group. After allocation, 3 patients in the nonenteral nutrition group required intervention according to individual attending physicians (Fig. 1). These 3 patients were given enteral elemental

Table 1 Patient profiles

	Enteral group N = 32	Nonenteral group N = 31	*P* value
Age, years	65.7 ± 9.2 (67, 36–79)	66.2 ± 13.2 (69, 37–82)	0.332
Gender			
Male	19	22	0.430
Female	13	9	
BMI	21.9 ± 3.9 (20.7, 15.8–35.6)	21.3 ± 2.4 (21.1, 17.9–27.1)	0.805
ASA-PS			
1	5	7	0.778
2	26	23	
3	1	1	
PNI	47.8 ± 8.5 (47.3, 29.6–66.4)	46.7 ± 4.5 (47.2, 36.8–57.5)	0.553
ICGR15	16.3 ± 5.5 (17.3, 5.1–24.8)	14.8 ± 5.9 (14.2, 3.5–27.9)	0.233
Non-neoplastic liver			
Normal	18	17	0.880
Chronic hepatitis	11	12	
Cirrhosis	3	2	
Diagnosis			
HCC	7	11	0.407
CCC	3	2	
CRLM	19	17	
Other	3	1	
Specifics of liver tumors	n=28	n=30	
Number	8.6 ± 7.0 (6, 1–26)	7.0 ± 5.9 (6.5, 1–21)	0.444
Size, mm	51.0 ± 28.0 (45.5, 22–140)	48.0 ± 42.8 (33, 5–160)	0.168

HCC, hepatocellular carcinoma; CCC, cholangiocellular carcinoma; CRLM, colorectal cancer liver metastases; BMI, body mass index; ASA, American Society of Anesthesiologists; PS, physical status; PNI, prognostic nutritional index; ICGR15, indocyanine green retention rate at 15 minutes. Except for numbers of patients, numbers without parentheses in the group columns are means ± SD. Numbers within parentheses in the group columns are medians followed by ranges.

nutrition by physicians (beginning on POD 1 for 1 patient and POD 2 for 2 patients) because they showed temporary elevations of serum bilirubin with or without ascites and were considered at risk for postoperative liver failure.

Background characteristics

The 2 groups were comparable with regard to age, gender, and neoplastic disease. Body mass index (BMI), ASA-PS grade, nutritional status calculated according to PNI, and histologic status of non-neoplastic liver also were comparable between groups. Among patients with primary or metastatic tumors, number and size of tumors were similar between groups (Table 1). Within the early enteral nutrition group, 1 donor patient for liver transplantation, 1 patient with cystadenoma, and 1 patient with retroperitoneal tumor were included in addition to the patients with primary or metastatic tumors. One patient with multiple liver cysts was included in the non-enteral nutrition group.

Surgical procedures and intraoperative results

Extent of liver resection was similar between groups. A laparoscopically assisted approach was used for 1 patient in each group. Second liver resections in 2-stage hepatectomies for multiple bilobar metastases from colorectal cancer or pancreatic neuroendocrine tumor also were distributed equally between groups. Combined resection of intrahepatic inferior vena cava (IVC) and reconstruction using a synthetic graft (Gore-Tex; WL Gore, Flagstaff, Arizona) was performed in 3 patients in the enteral group and 1 patient in the nonenteral group. Resection of the main trunk of the portal vein with end-to-end reconstruction was performed for 1 patient in each group. Duration of operation, intraoperative blood loss, and incidence of blood transfusion also were similar between groups (Table 2).

Postoperative course and incidence of infectious complications

Early oral diet was commenced in 65% of the patients on POD 1, and 79.3 % on POD 2. However, the average dietary intake was only 38.7 ± 3.6 % on POD 1. Three patients in the nonenteral nutrition group were given enteral nutrition because of temporary elevation of serum bilirubin with or without ascites as described previously (conversion rate, 3/31, or 9.7%). However, these bilirubin elevations did not satisfy the ISGLS definition of liver failure because they occurred before POD 5.[17]

One patient in each group died of liver failure within 90 days of liver resection. In the enteral group, 16 patients (50%) experienced postoperative complications, as did 17 patients (54.8%) in the nonenteral group. In the enteral group, incidence and severity of postoperative complications were grade I in 2 patients (6.3%), grade II in 11 (34.4%); 1 patient (3.1%) each had complications representing grades IIIa, IV, and V. In the nonenteral group, the distribution was 2 (10.3%), 5 (17.5%), 7 (7.2%), 2 (1.0%), and 1 (1.0%), respectively. Severe complications considered at least grade III occurred more frequently in the nonenteral

Table 2 Hepatectomy procedures and operative variables

	Enteral group N = 32	Nonenteral group N = 31	*P* value
Extent of Hx			
Bisections	7	5	0.516
Bisections + partials	5	2	
Hemiliver	10	15	
Hemiliver + partials	3	4	
Ext. hemiliver	4	3	
Ext. hemiliver + partials	1	2	
Trisections	2	0	
Concomitant procedures			
Lap-assisted	1	1	0.908
Staged Hx	9	5	
IVC resection	3	1	
PV resection	1	1	
Duration of operation, min	429.1 ± 156.8 (372, 225–878)	435.0 ± 137.1 (442, 148–776)	0.496
Intraoperative bleeding, L	0.95 ± 1.25 (0.46, 0.05–6.89)	0.78 ± 0.57 (0.70, 0.05–2.84)	0.517
Blood transfusion			
Administered	8 (25.0%)	5 (16.1%)	0.536

Hx, hepatectomy; Lap-assisted, laparoscopy assisted; IVC, inferior vena cava; PV, portal vein. Except for numbers of patients, numbers without parentheses in the group columns are means ± SD. Except for percentages, numbers within parentheses in the group columns are medians followed by rages.

Table 3 Short-term outcome

	Enteral group N = 32	Nonenteral group N = 31	*P* value
Mortality (≤90 days)	1 (3.1%)	1 (3.2%)	>0.999
Morbidity	16 (50.0%)	17 (54.8%)	0.803
Dindo–Clavien class			
I	2	2	0.172
II	11	5	
IIIa	1	7	
IVa	1	1	
IVb	0	1	
V	1	1	
Hospital stay, days	20.2 ± 15.6 (16.5, 7–87)	19.3 ± 18.0 (13, 7–82)	0.188

Except for numbers of patients, numbers without parentheses in the group columns are means ± SD. Except for percentages, numbers within parentheses in the group columns are medians followed by ranges.

Table 4 Details of postoperative complications

Complication	Enteral group N = 32	Nonenteral group N = 31
Liver-related	3	8
Biliary fistula	0	3
Ascites	0	1
Liver failure		
A	1	0
B	1	2
C	1	2
Infectious	11	12
Superficial/deep SSI	1	3
Organ/space SSI	2	3
Remote infection	0	1
Prolonged antibiotics	8	5
Others	3	7
Intestinal obstruction	1	3
Intestinal perforation	0	1
Respiratory disorder	1	0
Renal failure	0	1
Pancreatitis	0	1
Lymphorrhea	0	1
Poor appetite	1	0

SSI, surgical site infection; Prolonged antibiotics, postoperative prolonged administration of antibiotics.

All numbers represent numbers of patients.

group (10/31 or 32.3%) than in the enteral group (3/32 or 9.4%; $P = 0.031$). Length of hospital stay did not differ significantly (Table 3).

As for details of complications, 17 complications occurred in 16 patients in the enteral group, including 3 liver-related complications, 11 infectious complications, and 3 other complications. In the nonenteral group, 27 complications occurred in 17 patients including 8 liver-related complications, 12 infectious complications, and 7 other complications (Table 4).

No significant difference in total incidence of infectious complications was evident, including both surgical site (both superficial/deep and organ/space) and remote infections, between the enteral group (3/32 or 9.4%) and the nonenteral group (7/31 or 22.6%, $P = 0.184$; Table 5).

Table 5 Infectious complications

	Enteral group N = 32	Nonenteral group N = 31	*P* value
Total	3 (9.4%)	7 (22.6%)	0.184
Superficial/deep SSI	1	3	
Organ/space SSI	2	3	
Remote infection	0	1	

SSI, surgical site infection.

Table 6 Postoperative liver functional parameters

	Enteral group N = 32	Nonenteral group N = 31	*P* value
Platelet count (10^4/mm^3)			
POD1	15.7 ± 6.7	15.5 ± 5.5	0.917
POD7	17.6 ± 6.6	18.4 ± 8.9	0.905
POD14	23.2 ± 9.9	23.8 ± 14.1	0.784
Alanine aminotransferase (IU/L)			
POD1	448.5 ± 416.8	289.7 ± 241.9	0.024
POD7	79.5 ± 39.8	66.7 ± 46.9	0.103
POD14	32.2 ± 20.9	30.2 ± 22.2	0.436
Aspartate aminotransferase (IU/L)			
POD1	613.8 ± 507.4	392.9 ± 281.7	0.009
POD7	33.7 ± 14.3	35.3 ± 19.3	0.911
POD14	29.8 ± 22.1	25.9 ± 11.3	0.766
Total bilirubin (mg/dL)			
POD1	1.65 ± 0.99	1.42 ± 0.87	0.266
POD7	1.23 ± 1.48	1.05 ± 1.08	0.150
POD14	0.80 ± 0.34	1.25 ± 3.33	0.115
Albumin (g/dL)			
POD1	3.17 ± 0.34	3.09 ± 0.42	0.628
POD7	3.42 ± 0.36	3.31 ± 0.41	0.249
POD14	3.52 ± 0.57	3.51 ± 0.48	0.923
INR			
POD1	1.35 ± 0.16	1.32 ± 0.16	0.299
POD7	1.18 ± 0.16	1.17 ± 0.12	0.964
POD14	1.21 ± 0.27	1.16 ± 0.15	0.882

Values presented as mean ± SD.

Hematologic and biochemical test results

Hematologic and biochemical test results such as white blood cell, hemoglobin, platelet count, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, cholinesterase, plasma cholesterol, triglycerides, prothrombin time, activated partial thromboplastin time, and retinol binding protein showed no differences between groups throughout the clinical course (Table 6). Serum albumin concentrations also did not differ between the enteral group (preoperative, 3.99 ± 0.54; POD 1, 3.18 ± 0.35; POD 7, 3.42 ± 0.36; and POD 14, 3.53 ± 0.57) and the nonenteral group (4.04 ± 0.35, 3.10 ± 0.43, 3.31 ± 0.41, and 3.51 ± 0.48, respectively; $P = 0.864$, $P = 0.629$, $P = 0.249$, and $P = 0.923$, respectively). However, percentages of reduced-state albumin were greater on POD 7 in the enteral group than the nonenteral group ($P = 0.004$), as they also were on POD 14 ($P = 0.165$). Preoperative percentages did not differ between groups ($P = 0.931$). Serum pre-albumin concentrations on POD 7 tended to be lower in the nonenteral group than in the enteral group ($P = 0.089$, Fig. 2).

Discussion

Although guidelines have recommended supplementation with an immuno-enriched diet before visceral surgery,[23] evidence is insufficient that enteral immunonutrition confers any clinical benefits beyond those of standard enteral nutrition, even in patients undergoing esophageal or gastric resection for cancer.[24] Further, enteral immunonutrition relies on foodstuffs, so costs of such enteral feedings including immunomodulating compounds are not covered by the Japanese health insurance system.

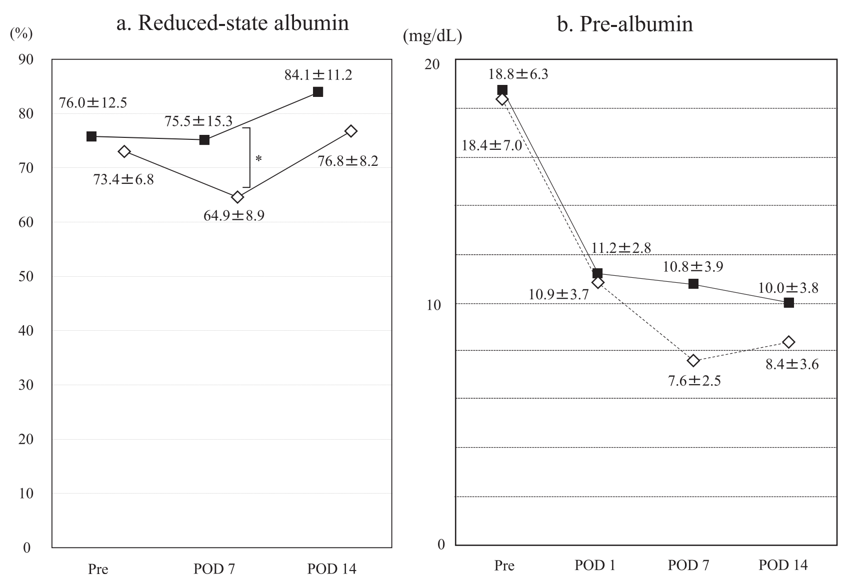

Fig. 2 Serial changes in postoperative oxidized albumin (a) and pre-albumin (b). Each value is the mean (±SD). *, $P <$ 0.01. ■, enteral group, n = 32; ◇, nonenteral group, n = 31. Pre, preoperative; POD, postoperative day.

Therefore, we used an elemental diet rather than an immune-enhanced or -modulated diet.

In the present study, prolonged antimicrobial therapy extending for 5 or more postoperative days was given frequently when WBC or CRP remained elevated even without an identified infection focus. The elevations may have reflected extensive liver resections. Therefore, even though prolonged antimicrobial therapy without an identified site of infection was included among postoperative complications in the Clavien–Dindo classification, we did not consider such elevations a study endpoint. The primary endpoint was the rate of infectious complications, which did not differ significantly between groups. Nonetheless, frequency of infectious complications tended to be less in the enteral nutrition than the nonenteral nutrition group, while frequency of grade III or more severe complications was significantly less in the enteral group than in the nonenteral group. Major surgery is a potent stimulus for systemic inflammatory responses which, if excessive and uncontrolled, can rapidly consume endogenous energy stores and induce immunologic dysfunction, eventually leading to postoperative complications including organ dysfunction. Enteral nutrition can promote immunity in the gut.[25] For example, macrophage function and secretory IgA concentrations are maintained by enteral nutrition.[25,26] Further, enteral nutrition can protect against gastrointestinal mucosal atrophy as well as functional and structural disruption,[27] and can even prevent bacterial translocation.[28,29] Thus, postoperative enteral nutrition in patients undergoing operations conveying high risk for postoperative complications can benefit from enhanced gut wall barrier function and modulation of inflammatory responses. Currently, the majority of the patients with liver resection may start an oral diet in the next day after hepatectomy. However, in the present study, patients who have started oral diet from the first day after operation was only about 60% of the whole and the average dietary intake was under 40%. Therefore, it seems that oral intake is not sufficient to support nutrition and immunologic function in the first few days after hepatectomy, and some additional nutritional supports are needed to make up for this insufficiency of oral intake.

The 10% of patients in the nonenteral group who received elemental nutrition because of temporary serum bilirubin elevations may have contributed to lack of significant differences between groups. Generally, nutritional supportive measures provide only limited benefit to patients with very severe hepatic insufficiency resulting from paucity of residual liver tissue or other major complications compromising hepatic function. However, some studies have reported enhancement of liver regeneration by enteral nutrition.[30] Further, during liver resection, ischemia-reperfusion injury and bile stasis rapidly damage bile duct epithelium, while enteral nutrition tends to prevent bile stasis.[31] As a result of these effects in addition to reduction of severe infectious complications in the enteral nutrition group, frequency of severe liver failure (grade B or worse) and liver-related complications in general tended to be smaller in the enteral nutrition group (2/32 or 6.3% and 3/32 or 9.4%) than in the nonenteral nutrition group (4/31 or 12.9%, $P = 0.426$; and 8/31 or 25.8%; $P = 0.107$).

Enteral nutrition can promote protein metabolism,[32] possibly by increasing amount and nutritional content of portal venous blood flow. Enhanced flow could accelerate turnover of proteins in the liver and regeneration in the remnant liver, especially after hepatectomy.[33] Serum pre-albumin undergoes more rapid turnover than albumin, showing a relatively short half-life of 48 hours without accumulation in the body or associated redistribution.[34,35] Almost all serum pre-albumin is synthesized in the liver, so blood concentrations depend greatly on the condition of the liver. A decreased pre-albumin concentration may reflect damage affecting liver function, which indicates risk of liver insufficiency after hepatectomy.[36] Further, pre-albumin has been considered an effective indicator of nutritional status in cancer patients.[34] In the present study, decreases in serum pre-albumin after hepatectomy were smaller in the enteral group than in the nonenteral group.

Oxidative stress also is a matter of concern during surgery, especially cardiovascular or liver surgery because of exposure to ischemia followed by reperfusion. Albumin, considered the major antioxidant substance in human serum,[37] has a half-life of 20 days.[37] After branched-chain amino acid (BCAA) dietary supplementation, the ratio of oxidized albumin to total albumin decreased significantly, while the proportion of reduced albumin increased significantly. No significant increase of total albumin concentration was observed.[38] In the present study, reduced albumin on POD 7 was lower in the enteral nutrition group than the nonenteral group, probably an effect of early introduction of enteral nutrition. Again, no difference in total serum albumin was evident between groups.

In conclusion, although the study did not show conclusive improvement in terms of the primary endpoint, some secondary endpoints showed favorable results in patients with early enteral nutrition. Specifically, patients undergoing major liver resection followed by early enteral nutrition did not show statistically significant prevention of infectious complications compared with a nonenteral nutrition group. However, some beneficial effects were seen, such as prevention of severe postoperative complications and improvement of nutritional status. Early enteral nutrition therefore may benefit patients undergoing major liver resections.

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