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ORIGINAL ARTICLE

Oral supplementation with carbohydrate- and branched-chain amino acid-enriched nutrients improves postoperative quality of life in patients undergoing hepatic resection

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Abstract The long-term outcomes of branched-chain amino acid (BCAA) administration in patients undergoing hepatic resection remain unclear. The aim of this study is to assess the impact of oral supplementation with BCAA-enriched nutrients on postoperative quality of life (QOL) in patients undergoing liver resection. A prospective randomized clinical trial was conducted in 96 patients undergoing hepatic resection. Patients were randomly assigned to receive BCAA supplementation (AEN group, $n = 48$) or a conventional diet (control group, $n = 48$). Postoperative QOL and short-term outcomes were regularly and continuously evaluated in all patients using a short-form 36 (SF-36) health questionnaire and by measuring various clinical parameters. This study demonstrated a significant improvement in QOL after hepatectomy for liver neoplasm in the AEN group based on the same patients' preoperative SF-36 scores ($P < 0.05$). Perioperative BCAA supplementation preserved liver function and general patient health in the short term for AEN group patients compared to those not receiving the nutritional supplement. BCAA supplementation improved postoperative QOL after hepatic resection over the long term by restoring and maintaining nutritional status and whole-body kinetics. This study was registered at http://www.clinicaltrials.gov (registration number: NCT00945568).

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Introduction

Liver resection is a potentially curative treatment for primary and secondary liver tumors. Recent advances in surgical techniques and perioperative management have made hepatic resection a safe procedure and the mainstay of curative treatment for liver malignancy (Ogata et al. 2007; Richter et al. 2009). However, hepatic surgery still carries a significant risk of postoperative morbidity due to the deteriorating liver function that might result from the inevitable reduction in functional liver mass (Okabayashi et al. 2008a, b, 2010).

Patients with chronic liver disease often reach a state of protein energy malnutrition (PEM) (Lautz et al. 1992; Caregaro et al. 1996), which affects patients' outcome following surgery as shown by quality of life (QOL) estimations (Alberino et al. 2001; Tajika et al. 2002; Moriwaki et al. 2004). Recent assessments of QOL integrate a biochemical heath model with a social science model that is based on the patient's subjective perception of functioning and wellbeing in a range of physical, mental, and social aspects of life (Marchesini et al. 2003). Since most liver neoplasms occur in patients with chronic liver disease, hepatic resection could potentially reduce QOL in these patients by further compromising liver function. Hence, it is important to consider the QOL as a treatment outcome in addition to operative mortality and long-term survival rates.

A few recent studies implicated an important role for nutritional support in the surgical management and postoperative QOL of patients who have undergone hepatic

resection for liver neoplasms (The San-in Group of Liver Surgery 1997; Meng et al. 1999). Specifically, our previous two retrospective studies demonstrated the clinical efficacy of nutritional supplementation with branched-chain amino acids (BCAAs) in patients with chronic liver disease who underwent hepatic surgery for liver neoplasms (Okabayashi et al. 2008a, b, 2010). Our preliminary case–control study suggested that the perioperative supplementation of BCAA-enriched nutrient mixture is of clinical benefit for nutritional support of patients undergoing liver resection. However, no studies have addressed the potential differences in long-term QOL in such patients with the perioperative oral administration of carbohydrate- and BCAA-enriched nutrient supplementation. This study, therefore, evaluated whether BCAA supplementation affects long-term self-estimated QOL and health in these patients on the randomized clinical setting.

Patients and methods

Patients

Of 100 people invited to take part in this prospective randomized study, 96 agreed to participate (Fig. 1). These patients were scheduled for elective liver resection to treat hepatocellular carcinoma or adenocarcinoma of the liver. Patient exclusion criteria were a body weight loss greater than 10% during the 6 months prior to surgery, the presence of distant metastases, or serious impairment of organ function due to respiratory, renal, or heart disease. All patients provided informed written consent prior to enrolment in the study, which was approved by the local ethics committee at the Kochi Medical School and carried out in accordance with the Helsinki Declaration. All studies were performed at the Kochi Medical School from April 2007 to October 2008.

Laboratory investigations and surgical parameters

All patients underwent a complete physical examination and provided a full clinical history with a focus on glucose metabolism including medication for the treatment of diabetes, fasting blood sugar levels, and hemoglobin A1c levels in plasma. Monitoring of the diabetes mellitus (DM) status of patients by a specialist clinician confirmed all diabetic subjects as Type 2. Blood samples from all patients were also analyzed for serum albumin, total bilirubin, total cholesterol, alanine and aspartate aminotransferases, peripheral blood cell count, prothrombin time, and retention of indocyanine green at 15 min (ICG15). The status of infection with hepatitis B and/or C virus (HBV, HCV) was assessed in all patients by testing for HBV antigen and HCV antibodies. Positive test results were confirmed by PCR analysis of sera for viral nucleic acid. Operation-related parameters and pathological state of the liver were also evaluated.

Methods

The patients were subdivided into two groups. One group was administered carbohydrate- and BCAA-enriched soft-powder nutrient mixture (Aminoleban EN, Otsuka Pharmaceutical, Tokyo; AEN group, $n = 48$), while the other group was given a conventional diet with no supplementation (control group, $n = 48$). The patients in the AEN group were given 50 g of Aminoleban EN orally twice a day, during the day and in the late evening. These patients were also educated by a dietician to adjust their total caloric energy intake by subtracting the equivalent of 420 kcal of food per day from their standard meals, so that all study patients received the same total caloric energy intake per day during the study period.

Supplementation with carbohydrate- and BCAA-enriched nutrient mixture

The present study used Aminoleban EN (100 g/day) for preoperative supplementation, commencing 2 weeks prior to surgery, and continuing for at least 6 months postoperatively with careful monitoring of compliance. A 100-g dose of Aminoleban EN contains 13.0 g of free amino acids, 13.0 g of gelatin hydrolysate, 1.0 g of casein, 62.1 g of carbohydrate, and 7.0 g of lipid, glycyrrhizin, and other components, for a total energy yield of 420 kcal.

Questionnaires

Patient health outcomes were monitored using a short-form 36 (SF-36) health sheet (Quality Metric, Lincoln, RI). The SF-36 is a reliable and scientifically validated measure of health outcomes (http//www.sf-36.org). In brief, SF-36 is designed to measure the full range of patient health and wellbeing via 36 multiple-choice questions (Ikegami et al. 2002).

Study endpoints

The primary endpoints of this study revolved around postoperative nutritional status, comprising various laboratory tests as well as postoperative QOL using the SF-36, including the changing trends of these nutritional evaluations, and whether the preoperative status was affected by perioperative administration of Aminoleban EN. Patient compliance was monitored prior to surgery and for at least 6 months after hepatic resection by both the attending

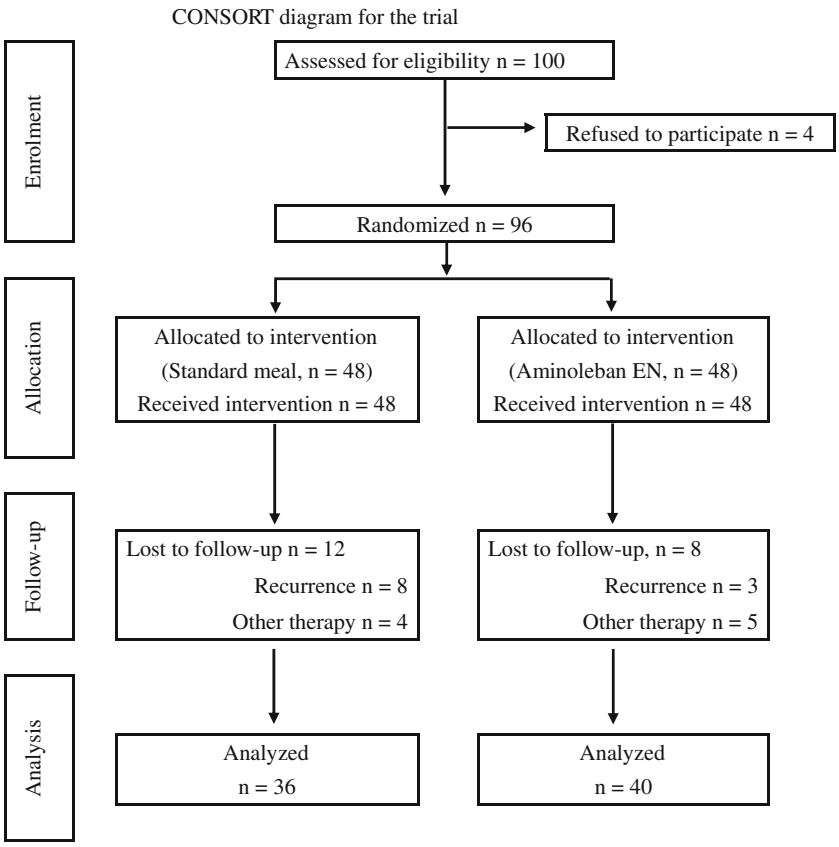

Fig. 1 CONSORT diagram for the trial

clinician and a registered dietitian at Kochi Medical School. The secondary endpoint was a comparison of measurements of body weight, arm muscle circumference (AMC) between patient groups.

Statistical analysis

Continuous variables are presented as mean ± SD. Dichotomous variables are presented as both number and percentage values. $P < 0.05$ was considered significant. Data were analyzed using Student's t test (two-tailed), with dichotomous variables analyzed by the χ^2 test (two-tailed) or Fisher's exact test (two-tailed), and the changing trends were evaluated using Cochran–Mantel–Haenszel statistics. All analyses were performed using SPSS® software (SPSS, Chicago, IL).

Results

Clinical parameters

Table 1 lists a range of preoperative clinical parameters for the 76 patients enrolled in the study. There were no significant differences between the AEN and control groups in clinical history, patient characteristics, or laboratory data, including nutritional parameters, liver function tests, and DM status. A history of DM was equally distributed between the groups.

All patients underwent a hepatectomy involving the curative resection of hepatic tissue for the removal of a tumor. Eight patients underwent a bisegmentectomy or extended hepatectomy (major hepatic resection) and 22 patients underwent a segmentectomy (minor hepatic resection). No patient showed a significant predisposition to a particular surgical procedure (Table 2). Operation times and estimated blood loss volumes did not differ significantly between the AEN and control groups. The final diagnoses of liver malignancy in the AEN group were hepatocellular carcinoma in 32 patients and adenocarcinoma in 8 patients, while the control group diagnoses revealed 26 patients with hepatocellular carcinoma and 10 with adenocarcinoma. Finally, there were no significant pathological differences in the background liver for each resected specimen between the groups.

Side effects of Aminoleban EN and operative mortality

The Aminoleban EN supplement was well tolerated in all patients including those with DM, despite the inclusion of dextrin. We evaluated completely that the compliance to diet, to balance the extra calorie and nitrogen provided by

Table 1 Preoperative clinical parameters

Characteristics	Control group ($n = 36$)	AEN group ($n = 40$)	P value
Age	65.1 ± 11.3	68.7 ± 7.6	0.11
Gender (female/male)	11/24	11/29	0.71
Body mass index	22.7 ± 3.2	23.6 ± 3.2	0.23
Previous medication for DM (%)	12 (33.3%)	11 (27.5%)	0.58
Cause of hepatic disease (%)			
HBV and/or HCV	16 (45.7)	22 (55.0)	
Alcohol	6 (17.2)	8 (20.0)	0.70
Unknown	13 (37.1)	10 (25.0)	
Child-Pugh Class (%)			
Class A	25 (71.4)	28 (70.0)	0.89
Class B	10 (28.6)	12 (30.0)	
Blood chemistry (normal range)			
Albumin (3.8–5.1 g/dl)	3.7 ± 0.5	3.7 ± 0.5	0.92
Total cholesterol (130–230 mg/dl)	172 ± 42	159 ± 32	0.18
Cholinesterase (200–440 U/l)	225 ± 66	215 ± 68	0.61
Prothrombin time (70–120%)	85.9 ± 15.6	83.1 ± 18.9	0.56
ICG15 (0–10%)	15.5 ± 12.1	17.2 ± 7.8	0.52
Hemoglobin A1c (4.0–5.5%)	5.4 ± 0.7	5.2 ± 0.6	0.21

DM diabetes mellitus, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *ICG15* the retention of indocyanine green at 15 min

Table 2 Operation-related parameters and pathological findings of the liver

Characteristics	Control group ($n = 36$)	AEN group ($n = 40$)	P value
Reason for liver resection			
Hepatocellular carcinoma	26	32	0.60
Adenocarcinoma	10	8	
Surgical procedure			
Hemihepatectomy	4	4	0.98
Segmentectomy of the liver	10	12	
Limited resection of the liver	22	24	
Operation time (min)	284 ± 100	281 ± 87	0.91
Estimated blood loss (ml)	676 ± 695	945 ± 827	0.18

nutritional supplementation, was checked and interviewed by a dietician, physicians, and surgeons at least once a month, when patients visited at our hospital. The postoperative clinical course was monitored in all patients until August 2009, with no differences detected among the total patient cohort in all-cause mortality rate. Operative mortality at 30 days following hepatic resection was also 0% in both groups. No patient in the present study was re-admitted to hospital due to operation-related causes.

Postoperative laboratory parameters

All baseline preoperative values were comparable between groups, while the postoperative monitoring revealed clear differences (Fig. 2). Serum albumin, total cholesterol, and cholinesterase levels were significantly different from baseline values in the AEN group, while the same measurements in the control group did not differ significantly from preoperative values even more than a year later. The serum albumin levels at postoperative 8 months, total cholesterol levels at postoperative 10 months, and serum cholinesterase levels at postoperative 12 months in the AEN group were significantly higher than comparable preoperative levels (Fig. 2). Furthermore, the changing trends of postoperative nutritional status, including albumin, total cholesterol and cholinesterase in the AEN group have been increasing significantly by Cochran–Mantel–Haenszel statistics, compared to the control group ($P \leq 0.05$).

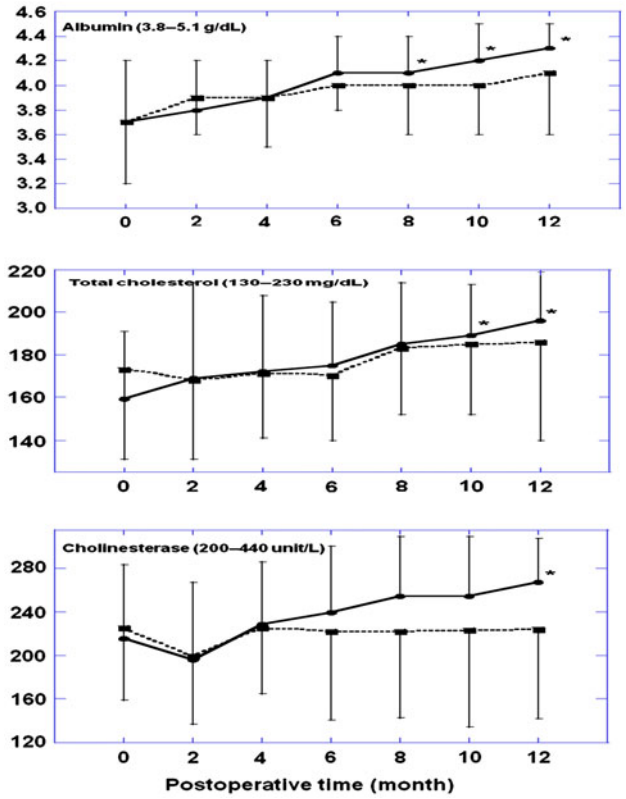

Fig. 2 Postoperative laboratory data in the group administered branched-chain amino acids-enriched nutrient mixture (AEN) (*solid line*) and the control group (*broken line*) (*$P < 0.05$, compared to preoperative levels)

Postoperative QOL in patients undergoing liver resection

Figure 3 shows the SF-36 health survey scores for eight parameters. As with the course of conventional anthropometry (Fig. 4), all scores decreased immediately after the operation. However, general health measures including perceptions of health and wellbeing, vitality, social functioning, and mental health improved by 6 months postoperative to at least preoperative levels in the AEN group. In a surprising result, all parameter scores subsequently and progressively improved compared to preoperative levels in the AEN group, while the control group showed no significant differences in postoperative QOL (Fig. 3).

Trends of conventional anthropometry

Changes in body weight and AMC were also evaluated in both groups relative to the corresponding preoperative values (Fig. 4). Body weight gradually increased in the AEN group compared to the control group over the 12-month observation period, although the differences from baseline values were not significant. In contrast, AMC was significantly higher than preoperative levels in the AEN group at postoperative 6 months and thereafter, while the control group values remained almost constant at the baseline levels (Fig. 4). Interestingly, the corresponding triceps skinfold thickness values were unchanged postoperatively in both groups (data not shown). Moreover, the changing trends of postoperative AMC in the AEN group have been increasing significantly by Cochran–Mantel–Haenszel statistics, compared to the control group ($P \leq 0.05$).

Discussion

Hepatocellular carcinoma and adenocarcinoma of the liver are among the most common malignant neoplasms worldwide. Unfortunately, palliative treatment is the only option for most patients with liver tumors even after curative surgical resection, due to the advanced stage of disease on presentation or the presence of severe underlying chronic liver disease. Due to advances in surgical methods and perioperative management, hepatic resection is often effective in prolonging patient survival despite the high recurrence rate. Liver surgery in these cancer patients was expected to lower the subsequent QOL, although a MEDLINE search of the English language literature revealed few reports that specifically addressed this issue (Poon et al. 2001; Lee et al. 2007; Banz et al. 2009; Okabayashi et al. 2010). It is probable that background liver status, due to liver cirrhosis, chronic liver disease, and/or liver damage due to chemotherapy for cancer, makes the evaluation of QOL in hepatectomized patients difficult. Perioperative nutritional support is an important issue that determines patients' outcome including their survival and QOL. In the liver surgery, one of current clinical interests is the use of BCAA, and several literatures have already been published as also referred to in this manuscript. However, information regarding QOL evaluation is quite limited, thus, making the present study a very important evidence for the effect of BCAA to improve postoperative QOL in patients with liver resection.

Patients with chronic liver disease have PEM and thus run short of proteins and energy (Lautz et al. 1992; Caregaro et al. 1996). Protein deficiency leads to a decrease in visceral proteins such as albumin and to decreased immunity (Miwa and Moriwaki 2004), while decreased energy leads to reduced fat and muscle mass. PEM therefore clearly affects the QOL and prognosis of patients with chronic liver disease, and reported incidences reach 65–90% (Moriwaki et al. 2004). Protein malnutrition in chronic liver disease is characterized by reduced serum albumin levels (visceral protein) and decreased skeletal muscle volume (muscular protein). The latter can be

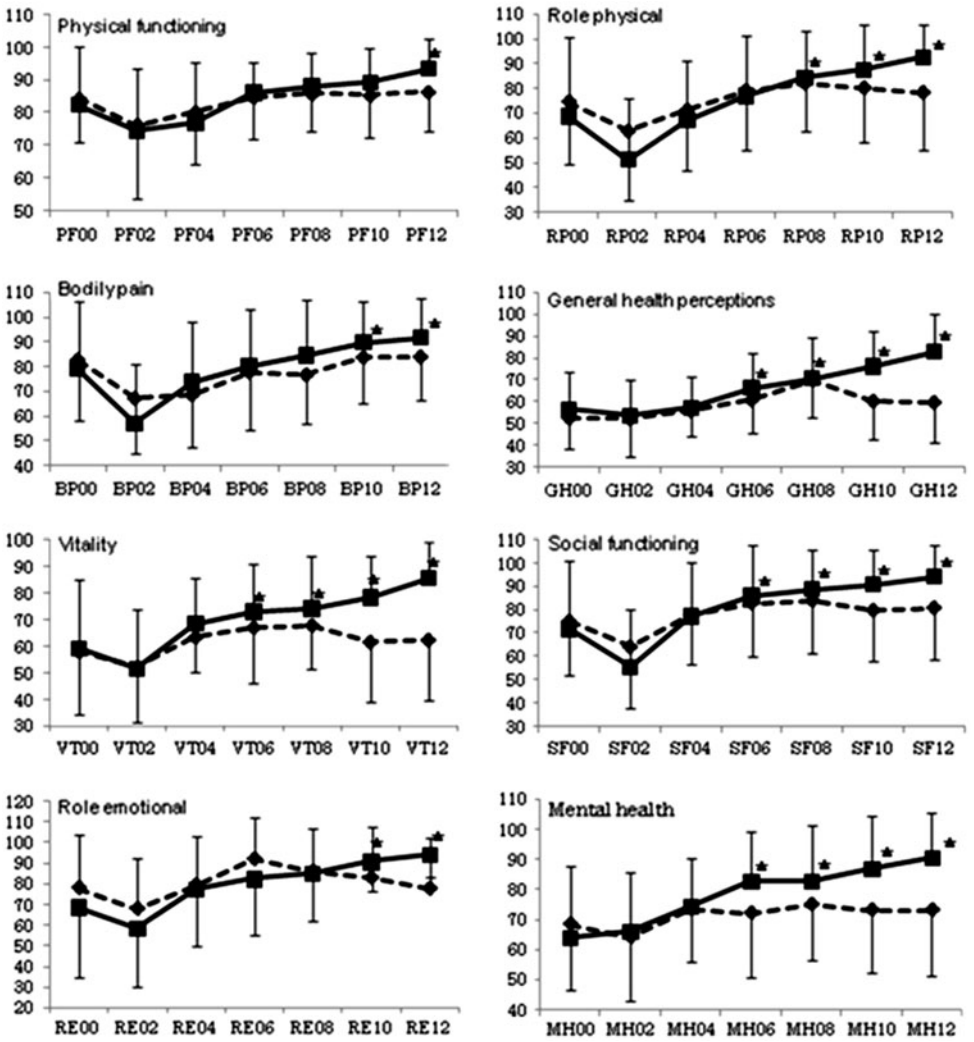

Fig. 3 Trends of Norm-based score by SF-36 in the group administered branched-chain amino acids-enriched nutrient mixture (AEN) (*solid line*) and the control group (*broken line*) (*$P < 0.05$, compared to preoperative score)

measured by conventional anthropometry as AMC (Moriwaki et al. 2004). Recent experimental and clinical data from several studies support the favorable effects of BCAA on protein malnutrition in chronic liver disease (Bianchi et al. 2005; Marchesini et al. 2005). It is, therefore, important to know whether perioperative oral supplementation with BCAA-enriched nutrients could improve postoperative QOL in patients undergoing a hepatectomy for liver cancer. To our knowledge, this study is the first to address this issue using SF-36.

In recent years, SF-36 has been used extensively for studying QOL in surgical patients worldwide (Sajid et al. 2008). The various domains in the SF-36 questionnaire evaluate QOL based on several important aspects of life (Sajid et al. 2008). Evaluating QOL specifically in patients undergoing surgery for liver tumors ideally needs a disease-specific subscale focusing on the special symptoms and problems related to the surgery in addition to the general QOL assessment criteria. The current study approached this issue using the SF-36 questionnaire alone to evaluate general health and QOL in hepatectomized patients.

This study showed significantly improved both blood chemical data and QOL in all domains of life at 12 months after hepatectomy for liver neoplasms, relative to the preoperative scores. Both blood chemical data and QOL assessed by SF-36 tended to deteriorate after postoperative about 2 months in each group. And they were improved in a preoperative state for postoperative 4 months in each group. These results might suggest that the effect of BCAA does not have under postoperative 4 months, when patients have chronic liver diseases. In the present study, patients received Aminoleban EN for perioperative supplementation, commencing 2 weeks prior to surgery, and continuing for at least 6 months postoperatively with careful monitoring of compliance. However, it should be evaluated how much is necessary in patients with chronic liver diseases undergoing liver resection prior to and after surgical management to preserve postoperative nutritional status and QOL. In patients undergoing hepatectomy for liver

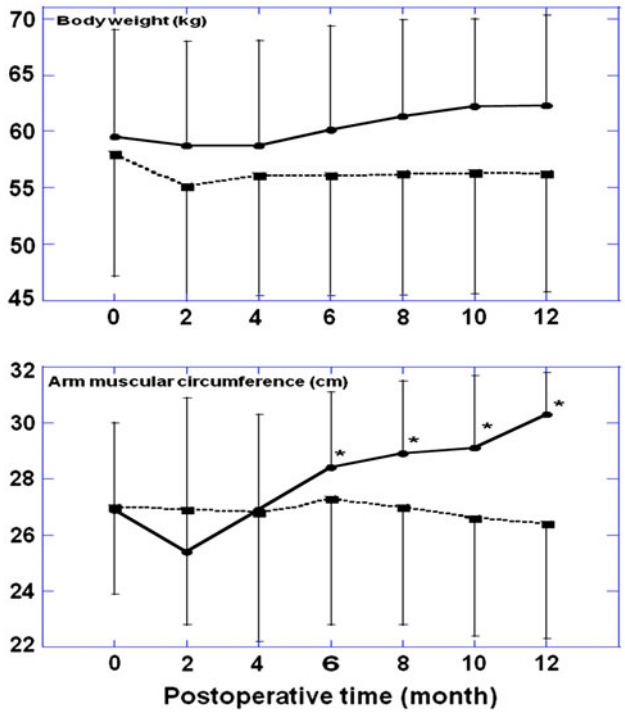

Fig. 4 Trends of body weight and arm muscular circumference in the group administered branched-chain amino acids-enriched nutrient mixture (AEN) (*solid line*) and the control group (*broken line*) (*$P < 0.05$)

tumors, perioperative oral supplementation of AEN clearly improved the patient's physical and mental wellbeing, and their general health perceptions, while also enhancing social wellbeing, bodily pain, vitality, and emotional wellbeing, from 12 weeks prior to surgery up to at least 6 months after surgery, and to a greater extent than removal of liver tumors alone. PEM largely affects patient outcomes by impacting QOL (Alberino et al. 2001; Tajika et al. 2002). In support of this, postoperative QOL and conventional anthropometry changes showed similar trends in the current series. Plasma amino acid analysis found that patients with chronic liver disease have decreased BCAA (Moriwaki et al. 2004), due to an amino acid metabolism imbalance and increased uptake of BCAA by muscle, and a plasma increase in aromatic amino acids due to reduced metabolism in the liver. Further analyses will be recommended about the concentration of BCAA, the BCAA-to-tyrosine ratio or Fischer's ratio (molar ratio of BCAAs and aromatic acids) to assess the intake of BCAAs. BCAA nutritional therapy, therefore, has a protein-sparing effect in patients with chronic liver disease, being directly available as an energy substrate by muscle, brain, heart, and liver, and consequently meeting the increased energy requirements of these patients (Blei and Cordoba 2001). Moreover, the perioperative oral supplementation of AEN improved both PEM and the balance between amino acid metabolism and synthesis in liver and muscle, and in turn had a positive effect on postoperative QOL.

Previous reports suggested that administering BCAA to patients with liver cirrhosis prolongs survival by improving the nutritional status of the patient and delaying mortality from liver failure (Miwa and Moriwaki 2004; Bianchi et al. 2005; Marchesini et al. 2005). Although the serum levels of albumin, total cholesterol, and cholinesterase decreased postoperatively in both groups of the present study, as expected in patients with chronic liver disease (Giovannini et al. 2006; Kogo et al. 2007; Pacella et al. 2009), the measurements were quickly restored in the AEN group to significantly higher levels than the preoperative baselines. Hepatocyte growth factor (HGF) is a pleiotropic factor able to modulate gene expression and to stimulate the proliferation and functions of many cell types, including hepatocytes. BCAA stimulates HGF production by hepatic stellate cells (Tomiya et al. 2004). Thus, in a similar manner to albumin, total cholesterol, and cholinesterase, liver regeneration might also be protected or rescued by administration of AEN. Preventing the reduced QOL and malnutrition often associated with the long-term treatment of liver cancer could, therefore, make this cancer treatment less difficult and reduce the rate of serious complications, thus improving patient prognosis (Poon et al. 2004).

Limitations of this study include the associated errors and biases inherent in a small study design. Large randomized control trials are recommended to further evaluate the benefit of branched-amino acids-rich nutrient support on the postoperative QOL of patients after hepatic surgery. In conclusion, nutritional support by BCAA effectively restored nutritional status and whole-body kinetics to patients following hepatic resection, and improved their long-term postoperative QOL.

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