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ORIGINAL ARTICLE

Oral supplementation of branched-chain amino acids reduces early recurrence after hepatic resection in patients with hepatocellular carcinoma: a prospective study

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Abstract
Purposes The long-term outcomes of branched-chain amino acids (BCAA) administration after hepatic resection in patients with hepatocellular carcinoma (HCC) remain unclear. This study assessed the effect of oral supplementation with BCAA on the development of liver tumorigenesis after hepatic resection in HCC patients.
Methods Fifty-six patients were randomly assigned to receive either BCAA supplementation (Livact group, $n = 26$) or a conventional diet (Control group, $n = 30$). Twenty-six patients in the BCAA group were treated orally for 2 weeks before and 6 months after hepatic resection. Postoperative tumor recurrence was continuously evaluated in all patients by measuring various clinical parameters.
Results There was no significant difference in the overall survival rate between the two patient groups; however, the recurrence rate at 30 months after surgery was significantly better in the Livact group in comparison to the Control group. Interestingly, the tumor markers, such as AFP and PIVKA-II, significantly decreased at 36 months after liver resection in the Livact group in comparison to the Control group.
Conclusions Oral supplementation of BCAA reduces early recurrence after hepatic resection in patients with HCC. This treatment regimen offers potential benefits for clinical use in such patients, even in cases with a well-preserved preoperative liver function.

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide. Recent advances in surgical techniques and perioperative management have made hepatic resection a safe procedure and the mainstay of curative treatment for liver malignancy [1, 2]. 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 the functional liver mass [3–5].

HCC also carries a considerable risk of tumor recurrence, with tumor stage (size, number, microvascular invasion, differentiation grade etc.) and any underlying liver disease important factors impacting the risk of recurrence [6]. Primary or secondary chemopreventive agents might improve the prognosis in HCC cases, since these patients are at high risk of HCC recurrence [7]. A few studies have identified candidate modalities including dietary supplementation with BCAA (leucine, isoleucine, and valine) that could potentially prevent progressive hepatic failure and improve event-free survival rates in patients with chronic liver disease [8, 9]. However, whether BCAA prevents liver carcinogenesis and the precise mechanisms of that prevention have not yet been explored in patients treated by surgical resection for liver cancer with a curative intent.

Two prospective studies demonstrated the clinical efficacy of nutritional supplementation with BCAA in patients with chronic liver disease that underwent hepatic surgery for liver neoplasms [5, 10]. They showed that BCAA

administration improves perioperative insulin resistance and postoperative quality of life after hepatic resection over the long term by restoring and maintaining nutritional status and whole-body kinetics. The present study assessed whether long-term oral administration of BCAA is effective with respect to improving nutritional state and preventing HCC recurrence after liver surgery.

Patients and methods

Patients

All 56 people invited to take part in this prospective cohort study agreed to participate (Fig. 1). These patients were scheduled for elective liver resection to treat HCC. Patient exclusion criteria were a body-weight loss >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 diabetes medication, fasting blood sugar levels, and hemoglobin A1c levels in plasma. 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. Surgery-related parameters and the pathological state of the liver were also evaluated.

Methods

Fifty-six patients with solitary HCC at the first treatment were analyzed. The patients were subdivided into two groups. One group was administered carbohydrate and BCAA granules (LIVACT, Ajinomoto Co. Inc, Tokyo, Livact group; $n = 26$), while the other group was given a conventional diet with no supplementation (Control group; $n = 30$). Control

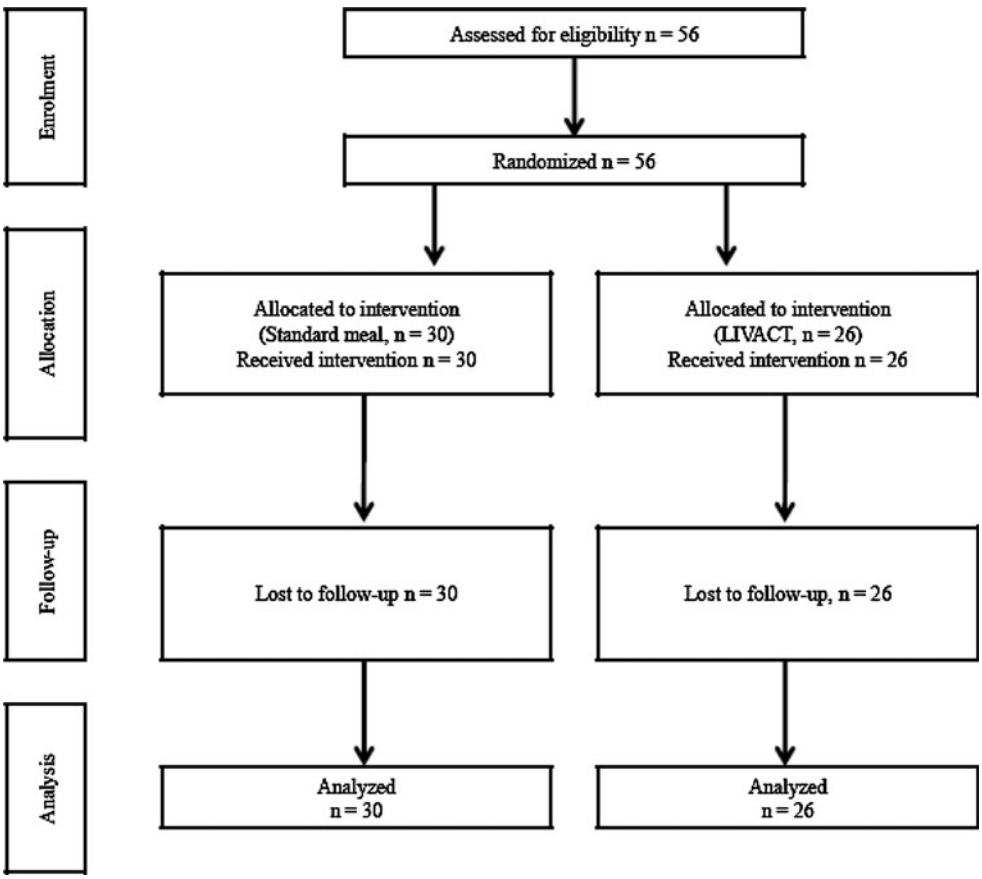

Fig. 1 CONSORT diagram for the trial

patients ate their usual meals and those in the BCAA group drank 4.74 g of Livact three times a day in addition to their meals. These patients were also educated by a dietician to adjust their total adequate caloric energy intake individually, so that all study patients received the same total caloric energy intake per day during the study period.

Composition of Livact

The Livact supplementation began 2 weeks prior to surgery, and continued for at least 6 months postoperatively with careful monitoring of compliance. The daily dose of Livact (4.74 g) contains 4 g of BCAA, specifically L-valine (1144 mg), L-leucine (1904 mg), and L-isoleucine (952 mg).

Study endpoints

The primary endpoint of this study was the HCC recurrence rate in patients with liver cancer after hepatic resection with intent-to-cure. Patient compliance was monitored prior to surgery and for at least 6 months after hepatic resection by both the attending clinician and a registered dietitian at Kochi Medical School. The secondary endpoint was a comparison of postoperative nutritional status, including blood chemistry data, body weight and arm muscle circumference (AMC) measurements and the changing trends of tumor markers in both α-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist (PIVKA)-II between patient groups. Data were collected before, during, and after surgery in a prospective computerized database and were analyzed retrospectively.

Statistical analysis

Continuous variables are presented as the mean ± SD. Dichotomous variables are presented as both the number and percentage values. $P < 0.05$ was considered to be 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). Where appropriate, values were expressed as the mean ± SD. Survival rates were generated using the Kaplan–Meier method and were compared using the log-rank test. The cumulative tumor recurrence rate (%) in patients with HCC was compared using a Mann–Whitney–Wilcoxon analysis. All analyses were performed using the SPSS® software package (SPSS; Chicago, IL, USA).

Results

Clinical parameters

Table 1 lists a range of preoperative clinical parameters for the 56 patients enrolled in the study. There were no significant differences between the Livact and Control groups in clinical history, patient characteristics, or laboratory data, which included nutritional parameters and liver function tests.

All patients underwent a hepatectomy involving the curative resection of hepatic tissue for the removal of a tumor. Twenty-four patients underwent either a bisegmentectomy or extended hepatectomy (major hepatic resection) and 32

Table 1 Preoperative clinical parameters

Characteristics	Control group ($n = 30$)	Livact group ($n = 26$)	P value
Age	64.5 ± 11.4	64.7 ± 9.8	0.748
Gender: male (%)	20 (66.7)	18 (69.2)	0.625
Body mass index (kg m^2)	22.5 ± 3.0	23.5 ± 3.5	0.255
Cause of hepatic disease (%)			
HBV and/orHCV	14 (46.7)	14 (53.8)	
Alcoholic	7 (23.3)	8 (30.8)	0.656
Unknown	9 (30.0)	4 (15.4)	
Child-Pugh class (%)			
Class A	25 (83.3)	21 (80.8)	0.920
Class B	5 (16.7)	5 (19.2)	
Blood chemistry (normal range)			
Albumin (3.8–5.1 g/dl)	0.8 ± 0.4	0.6 ± 0.3	0.268
Total bilirubin (0.3–1.1 mg/dl)	0.8 ± 0 4	0.6 ± 0.3	0.268
Cholinesterase (200–440 U/l)	213 ± 68	196 ± 83	0.268
Platelet counts (14.5–34 × 10^4 Ul)	20.1 ± 10.3	18.1 ± 10.5	0.351
Prothrombin time (70–120 %)	84.6 ± 15.4	76.0 ± 12.6	0.053
ICG 15 (0–10 %)	15.2 ± 12.4	19.1 ± 9.3	0.290
Hemoglobin Ale (4 0–5.5 %)	5. 9 ± 1.2	5.8 ± 1.1	0.873

HBV hepatitis B virus, *HCV* hepatitis C virus, *ICG 15* the retention of indocyanine green at 15 min

Table 2 Surgery-related parameters, postoperative complications, and length of hospitalization

Characteristics	Control group ($n = 30$)	Livact group ($n = 26$)	P value
Surgical procedure (%)			
Major liver resection	14 (46.7)	10 (38.5)	0.536
Limited resection of the liver	16 (53.3)	16 (61.5)	
Operation time (min)	293 ± 97	262 ± 72	0.202
Estimated blood loss (ml)	716 ± 704	492 ± 329	0.480
Postoperative complication (%)			
Ascites	1 (3.3)	2 (7.7)	0.592
Surgical site infection	3 (10.0)	2 (7.7)	0.867
Pathologic findings			
Size of the tumor (cm)	4.1 ± 2.4	4.1 ± 2.0	0.938
Differentiation (well moderately poorly)	11/19/0	11/14/1	0.950
The rate of microvascular invasion (%)	20.0	30.7	0.536
Background of the liver (Ch/Lc)	7/23	10/16	0.349
Hospitalization (days)	16 ± 7	13 ± 3	0.054
Recurrence periods (months)	14.8 ± 12.8	23.1 ± 15.5	0.107

Ch chronic hepatitis, *Lc* liver cirrhosis

patients underwent a segmentectomy (minor hepatic resection). No patient showed a significant predisposition to a particular surgical procedure (Table 2). The operation times and estimated blood loss volumes did not differ significantly between the Livact and Control groups. Finally, there were no significant pathological differences, including the size of the tumor, HCC differentiation, and the incidence of microvascular invasion, in the background of the liver for each resected specimen between groups (Table 2).

Side effects of Livact and operative mortality

The Livact supplement was well tolerated in all patients. 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. Surgical 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 surgery-related causes.

Overall survival and the cumulative tumor recurrence rate

Figure 2 shows the overall survival curves and the cumulative rate of HCC recurrence for the two patient groups at the time of data analysis. The median follow-up time after the first operation was 36.0 months (range 6–50 months) in the Control group and 39.5 months (7–48 months) in the Livact group. The 1- and 4-year survival rates were 96.2 and 83.9 %, respectively, for the Livact group, and 93.3 and 89.6 %, respectively, for the Control group. These results indicated no significant difference in survival rate between the groups. The entire cumulative rate of tumor recurrence in patients with HCC after curative resection for liver cancer was 83.5 %. Interestingly, patients in the Livact group showed a cumulative rate of HCC recurrence at 30 months after liver surgery of 28.5 %, while this rate was 55.7 % in the Control group, and the difference was significant at this follow-up point.

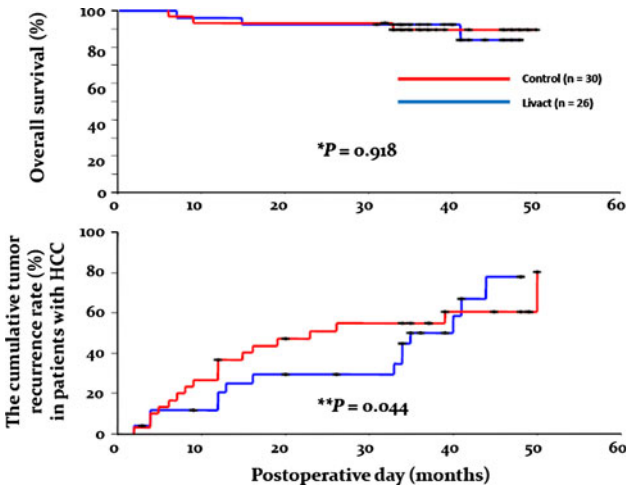

Fig. 2 Postoperative overall survival data and the cumulative tumor recurrence rate (%) in patients with HCC in the group administered branched-chain amino acids granules (Livact group) (*blue line*) and the Control group (*red line*). *Survival rates were generated using the Kaplan–Meier method and were compared using the log-rank test. **The cumulative tumor recurrence rate (%) in patients with HCC was compared using a Mann–Whitney–Wilcoxon analysis (color figure online)

Postoperative laboratory data and conventional anthropometric trends

Figure 3 indicates the trends in postoperative laboratory data and conventional anthropometry measures between the groups. All baseline preoperative values were

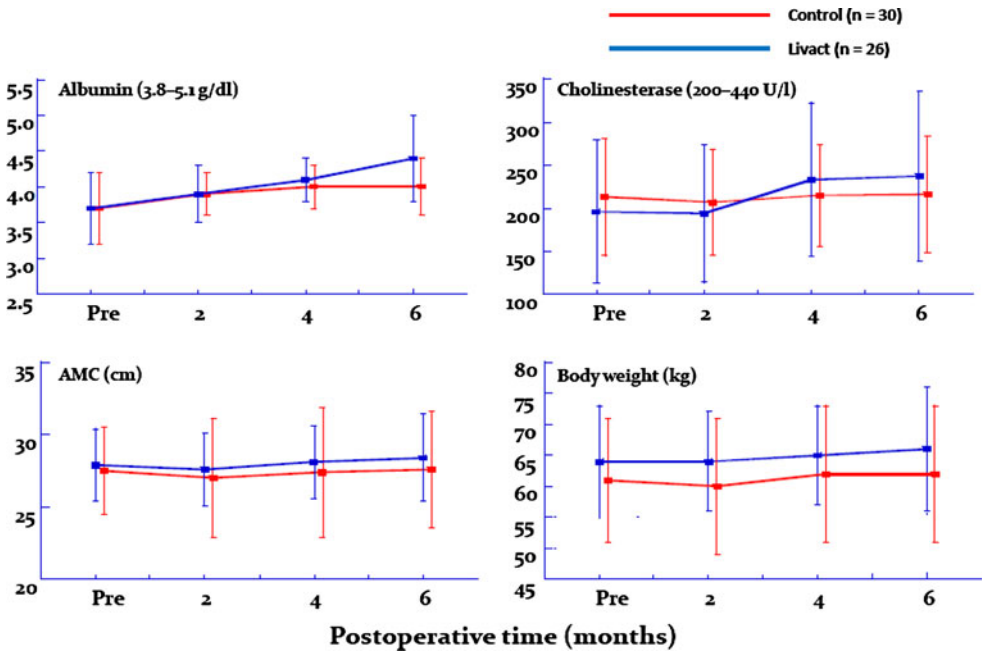

Fig. 3 Postoperative laboratory data and conventional anthropometry trends in the group administered branched-chain amino acids granules (Livact group; *blue line*) and the Control group (*red line*). *AMC* arm muscle circumference (color figure online)

comparable (Table 1) and there was no significant difference in these parameters between the groups before the operation or at 6 months after liver surgery. However, it is noteworthy that these parameters tended to improve in the Livact group at 6 months after hepatic resection for HCC in comparison to the Control group, although the differences did not reach statistical significance.

Changes in the body weight and AMC were also evaluated in both groups relative to the corresponding preoperative values (Fig. 3). Body weight gradually increased in the Livact group in comparison to the Control group over the 6-month observation period, although the differences from baseline values were not significant. AMC was also gradually restored in the Livact group in comparison to the Control group over the 6-month observation period, although the differences from baseline values were not significant.

Changing trends of the tumor markers

Figure 4 indicates the changing trends in the postoperative tumor markers such as both AFP and PIVKA-II between the groups. All baseline preoperative values were comparable (Fig. 4). These parameters were significantly reduced in the Livact group at 36 months after liver surgery for HCC in comparison to the Control group ($P < 0.05$).

Recurrence

Recurrence was evaluated in all patients who were recruited in the current study. Twenty-four of the 56 patients (43 %) showed no recurrence. The major sites of recurrence were the remnant liver (31 patients), bone (one patient), and lymph node

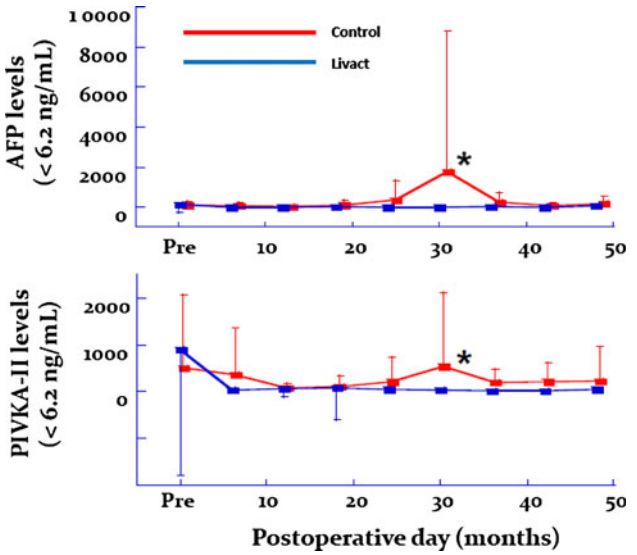

Fig. 4 Changing trends of tumor marker both AFP and PIVKA-II in the group administered branched-chain amino acids granules (Livact group) (*blue line*) and the Control group (*red line*) (*$P < 0.05$). *AFP* α-fetoprotein, *PIVKA* protein induced by vitamin K absence or antagonist (color figure online)

(one patient). The median time to the event in cases of recurrence was <2 years. The time to recurrence seemed to be shorter in the Control group than in the Livact group (Table 2).

Discussion

HCC is the fifth most common malignancy and the third leading cause of cancer-related death worldwide. Recent

improvements in surgical techniques and perioperative care have significantly reduced operative mortality and, to some extent, have improved the long-term survival of HCC patients after resection [11]. Nonetheless, the long-term prognosis after the surgical resection of HCC remains unsatisfactory, because of a high recurrence rate and lack of effective adjuvant therapy [6]. Unfortunately, however, the current study found no significant differences in the overall survival rate in patients with liver cancer after hepatic resection with intent-to-cure between the two groups.

Preventing recurrence after curative treatment of HCC remains a major challenge for the management for liver cancer [12]. This is particularly important during the early postoperative period since recurrence within 2 years after surgery is a poor prognostic indicator among early-recurrence cohorts of HCC patients [13]. The present study found reduced rates of HCC recurrence at 30 months after curative surgery with an oral supplementation of BCAA. Interestingly, tumor markers, including AFP and PIVKA-II levels were significantly reduced at 36 months after hepatic resection for liver cancer in the Livact group in comparison to the Control group. These results might suggest that the early-recurrence of HCC after curative resection for primary liver cancer was controlled by the supplementation of BCAA, because the period to recurrence seemed to be shorter in the Control group than in the Livact group. Several recent studies suggest that long-term supplementation with BCAA can inhibit hepatocarcinogenesis, especially in overweight or obese patients [7, 12, 14]. BCAA exerts multiple pharmacological activities; however, the mechanisms underlying this possible prevention of tumorigenesis in HCC remain unknown.

One possible mechanism is that BCAA is a potentially effective and critical candidate for improving insulin resistance [5, 15, 16]. Experimental studies using rodents found that BCAA induces glucose uptake in skeletal muscle, adipocytes, and hepatocytes, while leucine and isoleucine promote glucose uptake in skeletal muscle in a rat model of liver cirrhosis induced by CCl_4 [15]. Such effects might result from the upregulation of the glucose transporters 4 and 1 (GLUT4 and GLUT1) and the rapamycin-dependent activation of glucose synthase in skeletal muscle. Clinically, both obesity and insulin resistance are strongly associated with the development of not only HCC but also colorectal cancer [7, 12, 17]. This theory is supported by the current findings that the onset of tumor recurrence after curative surgery for HCC was delayed in the Livact group in comparison to the Control group. Interestingly, among the beneficial effects of BCAA shown in all reports, improving insulin resistance might be crucial in preventing the development of obesity-related liver tumorigenesis. However, all patients in the current study had a BMI within the normal range, suggesting that the beneficial effect of BCAA on both insulin resistance and tumorigenesis occurs in obese and non-obese patients with HCC.

Second, angiogenesis is a key process in tumor growth, and vascular endothelial growth factor (VEGF), which stimulates angiogenesis in a paracrine fashion, seems to be essential for the progression of various solid tumors [18, 19]. BCAA treatment markedly inhibits the development of preneoplastic lesions, as well as suppressing neovascularization and VEGF expression in the liver. BCAA administration also significantly suppressed glucose- and insulin-induced in vitro angiogenesis in the presence of endogenous VEGF expression [7]. The current study showed no significant difference in the cumulative rates of HCC recurrence at 4 years after surgical treatment between the BCAA-treated and Control groups (Fig. 2), despite patients receiving Livact for 6 months postoperatively. Therefore, the current results suggest that BCAA could positively impact hepatocarcinogenesis by improving insulin resistance and suppressing angiogenesis in HCC patients that continue the oral supplementation postoperatively following curative surgery.

Third, malnutrition due to hypoalbuminemia could also impact the high recurrence rates in HCC patients after hepatic resection. Indeed, hypoalbuminemia is an independent unfavorable factor in overall survival rate and/or recurrence rate for HCC [20]. Recent studies indicated that long-term supplementation with BCAA, especially in patients with chronic liver disease and/or liver cirrhosis, improves nutritional status and quality of life in terms of ameliorating hypoalbuminemia, as well as event-free survival [21–24]. However, the present study enrolled patients with HCC whose liver function and nutritional status were well preserved and in whom the tumor status was at an early stage, ensuring excellent curative treatment. Specifically, 82.1 % of the total patient cohort belonged to Class A according to the Child-Pugh classification, and preoperative liver function was well preserved.

This study had some limitations associated with errors and biases inherent in a small study design, and large randomized control trials are recommended to further evaluate BCAA with respect to the recurrence rate in patients after resection. This study revealed no significant differences in either the postoperative nutritional status or anthropometric trends between the patient groups, and this suggests that long-term supplementation with BCAA could inhibit hepatocarcinogenesis in both HCC patients with chronic liver disease and in those with a less-damaged liver. Further investigations are also needed to determine the optimal length of oral BCAA treatment to improve long-term survival and recurrence rates. One to two years of BCAA treatment after hepatic resection may be needed

to achieve better surgical results, based on the 6-month regimen used in this study.

In conclusion, the oral supplementation of BCAA reduces early tumor recurrence after hepatic resection in patients with HCC. This treatment regimen has the potential to clinically benefit patients with HCC, even when the preoperative liver function is well preserved.

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Conflict of interest All authors have no conflicts of interest to declare.

References

1. Ogata S, Belghiti J, Varma D, Sommacale D, Maeda A, Dondero F, et al. Two hundred liver hanging maneuvers for major hepatectomy: a single-center experience. Ann Surg. 2007;245:31–5.
2. Richter S, Kollmar O, Schuld J, Moussavian MR, Igna D. Chirurgische Arbeitsgemeinschaft OP-Technik und OP-Strukturen (CAOP) of the Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie. Randomized clinical trial of efficacy and costs of three dissection devices in liver resection. Br J Surg. 2009;96:593–601.
3. Okabayashi T, Nishimori I, Sugimoto T, Maeda H, Dabanaka K, Onishi S, et al. Effects of branched-chain amino acids-enriched nutrient support for patients undergoing liver resection for hepatocellular carcinoma. J Gastroenterol Hepatol. 2008;23:1869–73.
4. Okabayashi T, Nishimori I, Sugimoto T, Iwasaki S, Akisawa N, Maeda H, et al. The benefit of the supplementation of perioperative branched-chain amino acids in patients with surgical management for hepatocellular carcinoma: a preliminary study. Dig Dis Sci. 2008;53:204–9.
5. Okabayashi T, Nishimori I, Yamashita K, Sugimoto T, Namikawa T, Maeda H, et al. Preoperative oral supplementation with carbohydrate and branched-chain amino acid-enriched nutrient improves insulin resistance in patients undergoing a hepatectomy: a randomized clinical trial using an artificial pancreas. Amino Acids. 2010;38:901–7.
6. Hanazaki K, Kajikawa S, Shimozawa N, Mihara M, Shimada K, Hiraguri M, et al. Survival and recurrence after hepatic resection of 386 consecutive patients with hepatocellular carcinoma. J Am Coll Surg. 2000;191:381–8.
7. Yoshiji H, Noguchi R, Kitade M, Kaji K, Ikenaka Y, Namisaki T, et al. Branched-chain amino acids suppress insulin-resistance-based hepatocarcinogenesis in obese diabetic rats. J Gastroenterol. 2009;44:483–91.
8. Muto Y, Sato S, Watanabe A, Moriwaki H, Suzuki K, Kato A, for the Long-Term Survival Study (LOTUS) Group, et al. Overweight and obesity increase the risk for liver cancer in patients with liver cirrhosis and long-term oral supplementation with branched-chain amino acid granules inhibits liver carcinogenesis in heavier patients with liver cirrhosis. Hepatol Res. 2006;35:204–14.
9. Iwasa J, Shimizu M, Shiraki M, Shirakami Y, Sakai H, Terakura Y, et al. Dietary supplementation with branched-chain amino acids suppresses diethylnitrosamine-induced liver tumorigenesis in obese and diabetic C57BL/KsJ-db/db mice. Cancer Sci. 2010;101:460–7.
10. Okabayashi T, Iyoki M, Sugimoto T, Kobayashi M, Hanazaki K. Oral supplementation with carbohydrate- and branched-chain amino acid-enriched nutrients improves postoperative quality of life in patients undergoing hepatic resection. Amino Acids. 2011;40:1213–20.
11. Fan ST, Mau Lo C, Poon RT, Yeung C, Leung Liu C, Yuen WK, et al. Continuous improvement of survival outcomes of resection of hepatocellular carcinoma: a 20-year experience. Ann Surg. 2011;253:745–58.
12. Moriwaki H, Shiraki M, Fukushima H, Shimizu M, Iwasa J, Naiki T, et al. Long-term outcome of branched-chain amino acid treatment in patients with liver cirrhosis. Hepatol Res. 2008;38:S102–6.
13. Chun JM, Kwon HJ, Sohn J, Kim SG, Park JY, Bae HI, et al. Prognostic factors after early recurrence in patients who underwent curative resection for hepatocellular carcinoma. J Surg Oncol. 2011;103:148–51.
14. Togo S, Tanaka K, Morioka D, Sugita M, Ueda M, Miura Y, et al. Usefulness of granular BCAA after hepatectomy for liver cancer complicated with liver cirrhosis. Nutrition. 2005;21:480–6.
15. Nishitani S, Takehana K, Fujitani S, Sonaka I. Branched-chain amino acids improve glucose metabolism in rats with liver cirrhosis. Am J Physiol Gastrointest Liver Physiol. 2005;288:G1292–300.
16. Kawaguchi T, Taniguchi E, Itou M, Sumie S, Oriishi T, Matsuoka H, et al. Branched-chain amino acids improve insulin resistance in patients with hepatitis C virus-related liver disease: report of two cases. Liver Int. 2007;27:1287–92.
17. Giovannucci E, Michaud D. The role of obesity and related metabolic disturbances in cancers of the colon, prostate, and pancreas. Gastroenterology. 2007;132:2208–25.
18. Murata K, Moriyama M. Isoleucine, an essential amino acid, prevents liver metastases of colon cancer by antiangiogenesis. Cancer Res. 2007;67:3263–8.
19. Eikesdal HP, Sugimoto H, Birrane G, Maeshima Y, Cooke VG, Kieran M, et al. Identification of amino acids essential for the antiangiogenic activity of tumstatin and its use in combination antitumor activity. Proc Natl Acad Sci USA. 2008;105:15040–5.
20. Poon RT, Fan ST, Lo CM, Liu CL, Lam CM, Yuen WK, et al. Improving perioperative outcome expands the role of hepatectomy in management of benign and malignant hepatobiliary diseases: analysis of 1222 consecutive patients from a prospective database. Ann Surg. 2004;240:698–708.
21. Poon RT, Fan ST, Yu WC, Lam BK, Chan FY, Wong J. A prospective longitudinal study of quality of life after resection of hepatocellular carcinoma. Arch Surg. 2001;136:693–9.
22. Marchesini G, Bianchi G, Merli M, Amodio P, Panella C, Loguercio C, Italian BCAA Study Group, et al. Nutritional supplementation with branched-chain amino acids in advanced cirrhosis: a double-blind, randomized trial. Gastroenterology. 2003;124:1792–801.
23. Muto Y, Sato S, Watanabe A, Moriwaki H, Suzuki K, Kato A, Long-Term Survival Study Group, et al. Effects of oral branched-chain amino acid granules on event-free survival in patients with liver cirrhosis. Clin Gastroenterol Hepatol. 2005;3:705–13.
24. Giovannini I, Chiarla C, Giuliante F, Vellone M, Ardito F, Nuzzo G. The relationship between albumin, other plasma proteins and variables, and age in the acute phase response after liver resection in man. Amino Acids. 2006;31:463–9.