

Cancer (Hepatocellular) and Perioperative Branch-Chain Amino Acids

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Kirk Hamilton: Can you please share with us your educational background and current position?

Takehiro Okabayashi: In 2007/08/01 I became assistant professor (sub-professor); 2003/01/01, assistant professor; 2002/06/01, chief resident at Kochi Medical School, Kochi, Japan; 1999/06/01, resident at National Cancer Center Hospital, Tokyo, Japan; 1997/04/01, resident at Kochi Medical School, Kochi, Japan; 1997/03, graduated at Kagawa Medical School, Kagawa, Japan.

KH: What got you interested in studying the role of branch-chain amino acids in surgical patients with hepatocellular carcinoma?

TO: Hepatocellular carcinoma (HCC) is one of the most common malignancies in the world. As a result of recent advances in surgical technology and peri-operative management, hepatic resection for HCC is safe and the mainstay of curative treatment for HCC. The association of post-operative morbidity with the surgical management of HCC results from the presence of underlying liver cirrhosis in the majority of patients with HCC. Hepatic surgery causes further deterioration of liver function due to the loss of functioning liver mass.

Patients with cirrhosis of the liver complicated with HCC are often in a state of protein energy malnutrition. A limited number of studies have indicated an important role for nutritional support in the surgical management of patients who have undergone hepatic resection for HCC. [Ref. The San-in Group of Liver Surgery. Long-term oral administration of branched chain amino acids after curative resection of hepatocellular carcinoma: a prospective randomized trial. *Br J Surg*. 1997;84: 1525-31; Ref. Meng WC, Leung KL, Ho RL, Leung TW, Lau WY. Prospective randomized control study on the effect of branched-chain amino acids in patients with liver resection for hepatocellular carcinoma. *Aust N Z J Surg*. 1999; 69: 811-5].

KH: Exactly what are the branch-chain amino acids and what are their main functions?

TO: Protein energy malnutrition is a common manifestation of liver cirrhosis with reported incidences as high as 65-90%. Chronic liver disease is characterized by an

amino acid metabolism imbalance leading to a plasma decrease in branched-chain amino acids as a result of enhanced uptake by muscle, and a plasma increase in aromatic amino acids due to reduced metabolism in the liver. The use of branched-chain amino acid nutrition therapy as an energy substrate has a protein-sparing effect in patients with liver cirrhosis as branched-chain amino acids can be utilized directly by muscle, brain, heart, and liver as an energy substrate, and may therefore have a beneficial effect in meeting the increased energy requirement of patients with liver cirrhosis and HCC. Moreover, it is reported that BCAA improve the metabolism of albumin and the whole body kinetics.

KH: Where did you come up with a dose of 13 gms of free amino acids daily? How were these amino acids given? Over what time frame?

TO: We used the branched-amino acid-rich soft-powder nutrient-mixture (AEN; Aminoleban EN™, Otsuka Pharmaceutical Co., Ltd., Tokyo) as a daily nutrient supplement for patients with HCC prior to surgery. The liver plays an important role in energy metabolism. Patients with cirrhosis lack adequate glycogen stores because of liver atrophy and therefore develop a severe catabolic state after fasting. It has been reported that, after an overnight fast, patients with cirrhosis have a marked decrease in glucose oxidation, with enhanced fat and protein catabolism similar to that observed in healthy subjects after 2 to 3 days of starvation. To avoid such nocturnal starvation, energy supplements have been developed and are recommended as late evening snacks in the current American Society for Parenteral and Enteral Nutrition and European Society for Clinical Nutrition and Metabolism guidelines.

KH: Were any amino acid assessments done before, during or after the therapy? What other biochemical tests were done?

TO: Laboratory tests, including serum levels of albumin, total bilirubin, cholineesterase, total cholesterol, alanine aminotransferase and aspartate aminotransferase, peripheral thrombocyte counts, prothrombin time, Child-Pugh classification, and the retention of indocyanine green at 15 minutes, were routinely evaluated.

KH: Can you tell us about your study and the basic results?

TO: As expected, peripheral lymphocyte count and serum albumin and total cholesterol levels decreased immediately after the operation (at POD 6 days) in both groups. There was no significant difference in these parameters between the two groups before the operation and at POD 6 days. It is noteworthy that, at POD 3 months, these parameters restored faster to levels comparable to those before the operation in the BCAA group than in the control group. At POD 3 months, the lymphocyte count and serum total cholesterol levels in the BCAA group were significantly higher than in the control group ($P < 0.05$).

The lymphocyte count and total cholesterol levels restored after the surgery significantly faster in the BCAA group than in the control group, resulting in a shorter duration of hospitalization for the BCAA group than for the control group. These findings suggest that the administration of BCAA are of great help to improve not only the nutritional status but also whole-body kinetics.

KH: Were there any side effects to the amino acid therapy? How was the patient compliance?

TO: We experienced no patients with side effects to BCAA during our series. Our previous study suggested that the perioperative supplementation of a BCAA enriched nutrient mixture is of clinical benefit and safe for nutritional support of patients surgically managed for HCC in chronic liver disease. Patients received AEN supplementation from 2 weeks before surgery to at least 6 months after surgery and compliance with AEN was carefully monitored. The compliance was very good.

KH: Who is a candidate for branch-chain amino acid therapy? Why only oncology patients with hepatocellular carcinoma versus other types of cancer?

TO: I considered that patients who did not score high enough in Child-Pugh A status and all patients with Child-Pugh B status should receive oral administration of BCAA not only for hepatocellular carcinoma but also other types of liver disease. Of course, I think that BCAA are useful and beneficial for patients with other types of carcinoma of the liver not only hepatocellular carcinoma.

KH: Would this therapy reduce health care expenditures since it appears to reduce hospital stay?

TO: Because findings from our study indicate that the administration of BCAA modulate a metabolic response preserving the liver function of patients with chronic liver disease, and, BCAA preserve postoperative liver function and the general condition of the patient resulting in a shorter duration of hospitalization compared to controls, I believe that supplementation with perioperative AEN in patients undergoing surgical management for HCC would reduce health care expenditures.

KH: Do you have any further comments on this very interesting subject?

TO: Most patients with HCC have underlying liver cirrhosis that is frequently associated with a state of protein energy malnutrition. An additional study we have done pending publication was to evaluate the clinical benefit of peri-operative supplementation of a branched-chain amino acid enriched nutrient-mixture for patients undergoing liver resection for hepatocellular carcinoma (HCC). One hundred-twelve patients with HCC who underwent hepatic resection were enrolled in this study. These patients were divided into two groups: 40 patients received peri-operative supplementation of branched-chain amino acid enriched nutrient-mixture (AEN group) and 72 patients did not (control group). Laboratory data, post-operative complications, the duration of hospitalization, and survival were assessed for each group and compared. The overall incidence of post-operative complications was lower in the AEN group (44.4%) than in the control group (17.5%) ($P=0.01$). Among the post-operative complications, surgical site infection and bile leakage was observed in 5% of patients in the AEN group and in 15.3% and 12.5% of patients in the control group, respectively. Ascites appeared after the surgery in 7.5% of patients in the AEN group and in 16.7% of patients in the control group. The duration of hospitalization was significantly shorter in the AEN group than in the

control group ($P<0.05$). This study strongly suggests that peri-operative supplementation of a branched-chain amino acid enriched nutrient-mixture is clinically beneficial in reducing the morbidity associated with post-operative complications and in shortening the duration of hospitalization of patients with chronic liver disease who undergo liver resection for HCC. This study is now being submitted for publication.

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