Branched-Chain Amino Acids: Metabolism, Physiological Function, and Application

Branched-Chain Amino Acid-Enriched Nutritional Support in Surgical and Cancer Patients

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ABSTRACT Prolonged surgical stress and advanced malignant disease lead to systemic catabolism characterized by depletion of muscle protein and oxidation of skeletal muscle BCAA. BCAA oxidation provides energy for muscle and other organs and is the precursor for amino acid synthesis to replenish alanine and glutamine depleted in catabolic states. Persistent excessive catabolism leads to skeletal muscle wasting, negative nitrogen balance, and immune compromise. BCAAs, especially leucine, stimulate protein synthesis, inhibit proteolysis (in cell culture models and in animals), and promote glutamine synthesis. A number of small and diverse clinical trials studied the effects of BCAA-enriched nutritional support in moderately to severely stressed surgical and cancer patients. The findings of these clinical trials have been inconsistent; some show improved nitrogen balance, increased skeletal muscle protein synthesis, and reduced skeletal muscle catabolism whereas others show no significant improvement. The value of these trials is compromised by small sample size, heterogeneous patients, poor study design, varying degrees of metabolic stress, and inappropriate endpoints. More recent trials that evaluate clinical outcomes in hepatocellular carcinoma patients show promising results; in addition to improving metabolic parameters, BCAA-enriched oral supplementation improved morbidity and quality of life in patients undergoing major liver resection and chemo-embolization. In summary, the role of BCAAs in the nutritional support of stressed surgical and cancer patients remains to be clearly defined, despite their potential beneficial biological properties. J. Nutr. 136: 314S–318S, 2006.

KEY WORDS: • branched-chain amino acids • total parenteral nutrition • TPN
• enteral nutrition • catabolism • cancer • surgical stress

The BCAA leucine, isoleucine, and valine are essential amino acids in humans. Exogenous BCAA, from dietary or intravenous sources, are needed for normal cellular function. All dietary amino acids, including BCAAs, are absorbed by the small intestinal epithelial cells via discrete amino acid carriers, transported to liver via the portal vein, and then released into the systemic circulation (1, 2). BCAAs are regulators of protein synthesis and degradation and serve as key precursors for glutamine and alanine synthesis. In addition, BCAA oxidation provides a key energy source for muscle (3, 4). BCAA oxidation is controlled in the short term by leucine transamination by-products (5) and in the long term by many physiological and pathological conditions such as starvation, diabetes, sepsis, cancer, uremia, and infection (6–11).

Weight loss and malnutrition are among the most common features observed in surgical and cancer patients with prolonged catabolic stress. Greater than 50% of hospitalized surgical patients are considered malnourished or at risk for malnutrition, and >50% of cancer patients experience weight loss. Cancer cachexia is the most frequently cited cause of morbidity and mortality (12). Maintenance of adequate nutritional support, however, including total parenteral nutrition and enteral nutrition, has been ineffective in correcting the nutritional derangements in many catabolic states. Glutamine supplementation improves nutritional parameters and morbidity in some surgical and cancer patients (13). BCAAs are regulators of protein metabolism and are also key metabolic precursors for glutamine and alanine synthesis. These properties of BCAA have promoted their use in nutritional support aimed at improving function and clinical outcomes in critically ill patients.

This article provides a short synopsis of BCAA metabolism in catabolic states and reviews clinical trials using BCAA-enriched nutrition supplementation in surgical and cancer patients.
Altered protein and amino acid metabolism in catabolic states

Catabolic states are characterized by increased energy consumption, negative nitrogen balance, increased glutamine utilization, and derangements in amino acid metabolism. Increased BCAA oxidation in skeletal muscle is one of the metabolic responses that compensates for the increased energy expenditure and glutamine consumption (14). Under normal conditions, BCAA oxidation in skeletal muscle provides 6–7% energy, but in highly catabolic states this can be as high as 20%.

In moderate, short-term stress, intracellular muscle protein and glutamine concentrations fall, whereas intracellular muscle BCAA concentrations increase, suggesting that increased proteolysis provides BCAA to drive glutamine biosynthesis (15). The newly synthesized and mobilized glutamine helps maintain the circulating plasma concentration and meet the increased demand for glutamine. During prolonged, severe stress, markedly increased glutamine utilization may exceed the body’s synthetic capacity, and severe muscle glutamine depletion may result. If the hypermetabolic state persists, muscle protein and BCAA reserves will eventually be depleted and irreversible damage may occur.

Intestinal BCAA absorptive capacity is also increased in stress states. Using isolated jejunal brush border membrane vesicles, Souba et al. observed a significant increase of intestinal leucine absorption across the brush border membrane in fibrosarcoma-bearing rats, rats with intra-abdominal inflammation and abscess, and acidic rats (W. W. Souba, unpublished data).

Effects of branched-chain amino acids in stress states

BCAAs play a vital role in regulating protein metabolism. Exogenous BCAAs, specifically leucine, stimulate protein synthesis and decrease protein degradation in isolated muscle preparations, perfused rat muscle, and in vivo oral administration. In laparotomized rats, Freund et al. (16) reported that BCAA-enriched total parenteral nutrition (TPN) solutions, as well as BCAA-only solutions, preserved nitrogen balance by decreasing muscle protein catabolism and amino acid efflux, and suggested that the muscle depends on the exogenous supply of BCAAs to satisfy its metabolic requirements.

Many of BCAA’s beneficial effects during catabolic states are related to the synthesis of glutamine, a key factor in maintaining vital organ function. BCAA oxidation is a key precursor for glutamine synthesis. In both normal and stressed animal models and humans, BCAA increases glutamine synthesis and glutamine release from skeletal muscle and elevates plasma glutamine concentration (17, 18). Many animal studies and clinical trials demonstrate that glutamine supplementation improves nitrogen balance and recovery from infection after various insults such as burns, radiation injury, severe surgical stress, sepsis, and cancer (5).

BCAA-enriched nutritional support in clinical practice

Because of the recognized potential beneficial effects of BCAA, a number of clinical trials have been performed to evaluate effects of BCAA-enriched nutritional supplementation on correcting catabolic derangement and clinical outcomes in surgical and cancer patients (19–33). The majority of early trials focused on nitrogen balance, skeletal muscle catabolism measured by 3-methylhistidine (3-MH) excretion, and plasma amino acid profiles and uptake. More recent trials also evaluated clinical outcomes, such as morbidity and mortality in hepatocellular carcinoma (30–33). However, most clinical trials were small and varied in the type and number of patients studied, the degree of stress patients experienced, the specific composition and duration of nutritional supplementation, and the study methodology used.

Results from these clinical trials have been inconsistent: some studies showed BCAA-enriched solutions, particularly leucine, improving nitrogen balance, reducing skeletal muscle catabolism, increasing skeletal muscle protein synthesis and liver albumin synthesis, and maintaining plasma amino-acid concentrations (19, 21, 22), whereas others showed no apparent benefits (20, 24, 25, 28).

A number of possible explanations for the variable results in clinical studies thus far may be considered. Evidence suggests that BCAA-supplemented nutrition may only play a role in severely catabolic patients. Most of the studies in which a positive response is documented include such patients, identified by objective criteria (e.g., urinary nitrogen excretion, oxygen consumption, blood glucose, and plasma lactate). Other factors that appear to be important and that vary in studies are the total dose of amino acids, as well as the dose of BCAA, and the use of adequate nonprotein calories, electrolytes, and micronutrients. In addition, ≥5 d or more are required, under normal circumstances, to reach a new plateau of urinary nitrogen excretion when the nitrogen intake is substantially altered; yet the majority of studies are performed over short time periods. Significant intra- and interpatient nitrogen variability may render inadequate the sensitivity of quantitative nitrogen balance measurement techniques. Serious criticisms have also been raised about the validity of isotopic methods for assessing amino acid kinetics due to the nonsteady state of the stressed patient, isotopic and reentry effects of the isotopes used, and evidence of possible defects in membrane transport of the isotopes during stress.

BCAA-enriched nutritional support in surgical patients

In a prospective randomized clinical trial, Freund et al. (19) studied the effects of BCAA on nitrogen balance and amino acid profile in patients who underwent surgical laparotomy. Thirty-five patients were randomized to receive control (5% dextrose only, n = 10), 22% BCAA (3% total amino acid + 5% dextrose, n = 9), 35% BCAA (3% total amino acid + 5% dextrose, n = 9), and 100% BCAA (3% total amino acid + 5% dextrose, n = 7) for 5 d. Total caloric intake and total protein intake were unequal among the control and BCAA groups. All patients in the 3 BCAA groups had better nitrogen balance (either in equilibrium or positive nitrogen balance) than the patients in the control group (P < 0.001), but there was no difference in nitrogen balance among the 3 different BCAA concentration groups. Weight loss between the patients in the control group and the BCAA groups was not statistically significant, although the BCAA groups had less weight loss or slight weight gain (100% BCAA group). Mean hospital stay was 19 d for patients receiving dextrose only (control group) and 17 d for patients receiving amino acids (P = NS). The plasma amino acid concentration profiles resembled that of the administered BCAA solution. The hypocaloric infusion could partially explain the poorer metabolic results in the control group.

Abbreviations used: TPN, total parenteral nutrition; 3-MH, 3-methylhistidine.
In a prospective study, Cerra et al. (20) evaluated the effect of BCAA on nitrogen balance and 3-MH excretion in a mixed population of surgical and trauma patients. Fifteen patients were randomly assigned to receive TPN containing 15.5% BCAA (n = 8) or TPN containing 50% BCAA (n = 7) for 7 d. All patients received an equal amount of nonprotein calories (35 kcal kg\(^{-1}\) d\(^{-1}\)) and protein (1 g kg\(^{-1}\) d\(^{-1}\)). Patients receiving 50% BCAA began with significantly worse nitrogen balance on d 0 (P < 0.05) and achieved significantly better nitrogen balance by d 3 compared with patients receiving 15.5% BCAA (P < 0.01). There was no statistically significant difference in nitrogen balance by d 6. There was no statistically significant difference in 3-MH excretion between the low and high BCAA groups on each study day. In this study of mostly mild to moderately stressed patients, defined by Cerra et al. (20) as baseline urinary nitrogen excretion of <10 g/d, the 2 groups may not have been comparable with significantly different baseline urinary nitrogen excretion (11.0 ± 8.6 g and 6.0 ± 4.0 g in the 50% BCAA and control groups, respectively).

In a separate, larger, double-blind study, Cerra et al. (21) again studied the effects of various BCAA concentrations on nitrogen balance and 3-MH excretion in a mixed population of surgery and trauma patients (n = 32). The total urinary nitrogen excretion on d 0 of the study was 6–23 g/d, indicating a significant stress in almost all patients. These patients were randomized to 4 groups (n = 8 each): TPN containing 15% BCAA (30 kcal kg\(^{-1}\) d nonprotein calories and 1 g kg\(^{-1}\) d protein), TPN containing 50% BCAA (30 kcal kg\(^{-1}\) d nonprotein calories and 1 g kg\(^{-1}\) d protein), TPN containing 20% BCAA (37 kcal kg\(^{-1}\) d nonprotein calories and 1.5 g kg\(^{-1}\) d protein), and TPN containing 47% BCAA (37 kcal kg\(^{-1}\) d nonprotein calories and 1.5 g kg\(^{-1}\) d protein). The authors reported that on d 3 patients who received TPN containing 50% BCAA and 47% BCAA had significantly better nitrogen balance than the patients who received TPN containing 15% BCAA. By d 7 the patients who received TPN containing 47% BCAA had significantly better nitrogen balance than the patients in all other groups. In addition, the patients who received the same amount of calories and protein but with higher BCAA (50% BCAA with 1 g kg\(^{-1}\) d protein or 47% BCAA with 1.5 g kg\(^{-1}\) d protein) had significantly better nitrogen balance than those receiving the same amount of calories and protein but with lower BCAA (15% BCAA with 1 g kg\(^{-1}\) d protein or 20% BCAA with 1.5 g kg\(^{-1}\) d protein). However, there was no statistically significant difference in 3-MH excretion among these groups.

In a prospective, randomized, double-blind, six-center trial, Cerra et al. (22) studied the effect of BCAA on nitrogen retention in surgically stressed patients. At least 30% of patients in both groups were significantly stressed with baseline urinary nitrogen excretion of >10 g/d. Eighty-seven patients were randomized to receive TPN containing 19% BCAA (5.1 amino acids, n = 34) and 44% BCAA (5.1 amino acids, n = 53) for 7 d. Although total caloric intake and total protein intake varied from day to day, there was no difference in the amount of calories or nitrogen administered between the 19% BCAA group and 44% BCAA group on any given study day. Patients who received 44% BCAA had better nitrogen balance for the same nitrogen intake by d 3–4.

In a prospective uncontrolled trial, Bower et al. (23) studied the effect of BCAA-enriched TPN on nitrogen balance and 3-MH excretion in postoperative patients. All patients (n = 20) received TPN containing 45% BCAA (4.25% amino acids, 30 kcal kg\(^{-1}\) d nonprotein calories and 1.6 g kg\(^{-1}\) d protein) for 7–14 d. Significantly better nitrogen balance, compared with baseline, was measured, starting at d 4 and continuing over the entire study period. There was no significant difference in 3-MH excretion throughout the study.

In a prospective randomized trial involving 15 elective gastrectomy and hemicolectomy patients, Jaing et al. (24) evaluated the effect of BCAA on nitrogen balance, 3-MH excretion, and plasma amino acid profiles. The patients were randomized to receive TPN containing 23% BCAA (n = 8) or TPN containing 40% BCAA (n = 8) for 10 d. All patients received 30 kcal kg\(^{-1}\) d nonprotein calories and 1.25 g kg\(^{-1}\) d protein. There was no statistically significant difference in nitrogen balance or 3-MH excretion between the groups. However, the plasma concentrations of leucine and valine were significantly increased 2 d after higher BCAA administration. In this study, the patients were only mildly stressed with baseline urinary nitrogen excretion of <5 g/d and the two groups may not have been comparable with higher baseline urinary nitrogen excretion in the BCAA group compared with the control group.

**BCAA-enriched nutritional support in cancer patients**

In a prospective study, Daly et al. (25) compared effects of 25% or 45% BCAA TPN solutions on nitrogen balance and forearm amino acid uptake in 8 patients undergoing cystectomy and ileal conduit for bladder cancer. Baseline urinary nitrogen excretion levels were <10 g/d in these mildly stressed patients as defined by Cerra et al. (20). The patients received 20 kcal kg\(^{-1}\) d nonprotein calories and 1.5 g kg\(^{-1}\) d protein for 7 d postoperatively. The authors reported that the nitrogen balance trend was favorable in the 45% TPN group (-1.4 ± 7.1 g/d vs. -14.2 ± 3.8 g/d 25% TPN), although the difference was not statistically significant. Uptake of forearm total amino acids and BCAA was significantly increased in the higher BCAA group, although no baseline flux measurements were reported.

In another separate trial, Bonau et al. (26) studied effects of BCAA on nitrogen balance and forearm skeletal muscle amino acids flux in patients who underwent radical cystectomy with ileal conduit. Thirteen patients were assigned to receive TPN (29 kcal kg\(^{-1}\) d nonprotein calories and 1.4 g kg\(^{-1}\) d protein) containing 25% BCAA (n = 6) or 45% BCAA (n = 7) for 7 d. No significant difference in nitrogen balance or forearm muscle total amino acids uptake was observed, although forearm muscle BCAA uptake was significantly higher in the 45% BCAA group.

Bonau et al. (27) performed a larger prospective but nonrandomized trial to study the effects of various compositions of BCAA (leucine, isoleucine, and valine) in TPN on nitrogen balance in 25 patients who underwent cystectomy with ileal conduit. Four treatment groups were studied: control (5% dextrose, n = 4), 25% BCAA-balanced solution (30 kcal kg\(^{-1}\) d nonprotein calories, n = 9), 45% valine-rich BCAA solution (30 kcal kg\(^{-1}\) d nonprotein calories), and 45% leucine-rich BCAA solution (30 kcal kg\(^{-1}\) d nonprotein calories). All TPN groups received 1.5 g kg\(^{-1}\) d protein whereas the control group received dextrose only for 7 d postoperatively. All TPN groups had significantly better nitrogen balance than the control group, although the hypocaloric infusion in the control group may partially account for this observation. Both 25% BCAA and 45% leucine-rich BCAA groups had more positive, albeit not statistically significant, cumulative nitrogen balance than the 45% valine-rich BCAA group; the 45% leucine-rich BCAA group had significantly better daily nitrogen balance than the 45% valine-rich BCAA solution; and the 3–4 d cumulative nitrogen balance in the 23% BCAA group was significantly better than in the 45% valine BCAA group. Nitrogen balance was not different between the 25% BCAA and 45% leucine-rich BCAA solution. The authors concluded that the amount of
leucine was more important than the amount of valine in the BCAA solution.

In a large prospective multicenter trial involving 16 Japanese institutes and 173 patients, Okada et al. (28) studied the effect of BCAA on nitrogen balance and 3-MH excretion in patients who underwent subtotal or total gastrectomy for gastric cancer. The patients were randomized to 4 groups: subtotal gastrectomy receiving 22.6% BCAA TPN (n = 39), subtotal gastrectomy receiving 36% BCAA TPN (n = 41), total gastrectomy receiving 22.6% BCAA TPN (n = 40), and total gastrectomy receiving 36% BCAA TPN (n = 40). All patients received 7 d of TPN (40 kcal/g protein) containing 36% BCAA TPN in both subtotal gastrectomy and total gastrectomy groups. However, the authors reported higher serum BCAA levels and lower aromatic amino acid levels in patients receiving 36% BCAA TPN in either the subtotal gastrectomy or total gastrectomy groups.

In a prospective randomized trial, Hunter et al. (29) evaluated the effect of BCAA-enriched TPN on protein kinetics in patients with intra-abdominal carcinoma. Nine malnourished patients were randomized to receive standard TPN (19% BCAA) or isocaloric (1.5 × basal energy expenditure/d) and isonitrogenous (1.2 g/g protein) BCAA TPN enriched TPN (50% BCAA) for 42 h. BCAA-enriched TPN increased leucine oxidation and decreased tyrosine oxidation in addition to stimulating synthesis of protein and albumin. The authors concluded that BCAA promoted protein synthesis and utilization.

Clinical trials with outcome studies in cancer patients

In a large study, Fan et al. (30) assessed clinical outcomes of 124 patients undergoing perioperative nutritional support for hepatocellular carcinoma. Sixty-four patients (39 with cirrhosis, 18 with chronic active hepatitis, and 7 with no associated liver disease) were randomly assigned to receive perioperative intravenous nutritional support (35% BCAA) for 14 d (7 d before surgery and 7 d after surgery) in addition to their oral diet, and 60 patients (33 with cirrhosis, 12 with chronic active hepatitis, and 15 with no associated liver disease) were randomly assigned to a control group (usual oral preoperative diet and dextrose fluid only postoperatively). A significant decrease of postoperative morbidity in the nutrition-supplemented group (34%) was observed compared with the control group (55%). The difference was mainly due to a reduction in septic complications in the perioperative-nutrition group (17% vs. control group 37%). There was also decreased use of diuretic therapy to control ascites in the perioperative-nutrition group (25%) compared with the control group (50%), and less weight loss in the perioperative-nutrition group (0 kg) compared with the control group (1.4 kg). There was, however, no significant difference in hospital mortality in the perioperative-nutrition group (8%) compared with the control group (15%, P = 0.30). In the postoperative period, there was no significant difference between the 2 groups in prothrombin time, serum bilirubin measurements, or liver-enzyme levels except for serum aspartate aminotransferase. Plasma glucose, serum urea, serum transferrin, serum prealbumin, and serum retinol-binding protein levels were significantly higher in the perioperative-nutrition group than in the control group on most of the postoperative days.

In a prospective trial to study the long-term effect of oral BCAA supplementation on patients who underwent major liver resection for hepatocellular carcinoma (31), 2–3 wk after surgery 75 patients were randomized to receive oral BCAA (Aminoleban EN 100 g/d containing 11 g/d BCAA; Otsuka Pharmaceutical Company, Japan) daily for 1 y, and 75 patients were assigned to a control group receiving normal oral diet only. Patients who received oral BCAA supplementation had better ascites and edema control and better performance status at 3 mo compared with the control group (P < 0.001). Patients who received the BCAA supplementation had greater body weight and better performance status throughout the 1 y period. No advantage in cumulative tumor recurrence (30 in BCAA group and 23 in control group) and survival rates (49% in BCAA group and 51% in control group) among the groups was reported through the 3-y follow up.

In a separate prospective randomized trial, Meng et al. (32) studied the effect of oral BCAA supplementation on clinical outcomes in patients who underwent hepatectomy for hepatocellular carcinoma. Twenty-one patients were randomly assigned to receive oral BCAA supplementation (Aminoleban EN 150 g/d containing 40 g/d protein and 5.5 g/d BCAA) in addition to normal diet (40 g/d protein) for 12 wk after surgery, and 23 were randomly assigned to receive a control isonitrogenous (80 g/d protein) and isocaloric normal diet (6300 kJ/d). The authors reported that patients who received oral BCAA supplementation had a shorter hospital stay (10 d vs. 16.5 d, P = 0.02) and quicker improvement of liver function in the early postoperative period. However, no significant difference in morbidity and mortality between the 2 groups of patients was observed.

In a trial involving patients with unresectable hepatocellular carcinoma, Poon et al. (33) investigated the effect of oral BCAA nutritional supplementation on morbidity and mortality in hepatocellular carcinoma patients who underwent transcatheter arterial chemoembolization. Forty-one patients received oral BCAA supplementation (Aminoleban EN 100 g/d containing 11 g/d BCAA) in addition to the usual diet, and 43 patients received the usual diet only for up to 1 y. The authors reported that patients who received oral BCAA supplementation had significantly lower overall morbidity (17.1% in BCAA group vs. 37.2% in control group), a significantly lower ascites rate (7.3% in BCAA group vs 23.2% in control group) and lower peripheral edema (9.8% in BCAA group vs 27.9% in control group). Significantly higher albumin, lower bilirubin, and better quality of life were also reported in the BCAA group. However, there was no difference in mortality.

Summary

The potential beneficial role of nutritional support that is enriched in BCAA, especially leucine, in surgical and cancer patients is still not clear, despite a better understanding of biological properties of BCAA in animals and in cell culture. The published clinical trials so far have been small and diverse and results have been inconsistent. Results from these less-than-optimal small trials, either positive or negative, cannot conclusively prove or disprove a beneficial effect of using BCAA-enriched nutritional support in surgical and cancer patients. Large prospective, randomized, well-designed clinical trials are needed to better define the role of BCAA in surgical stressed and cancer states.

LITERATURE CITED