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How to select BCAA preparations

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Abstract

In Japan, oral branched-chain amino acid (BCAA) preparations are used in nutritional therapy for correcting disorders of protein and amino acid metabolism in patients with liver cirrhosis. There are two forms of oral BCAA preparations: enteral nutrition products for liver failure (or elemental nutrition products for liver cirrhosis) and oral BCAA granular products. Granular products are indicated for patients with uncompensated liver cirrhosis who have no dietary restriction and hypoproteinemia. Enteral nutrition products are indicated for patients who have a history of hepatic encephalopathy and exhibit protein intolerance. In clinical practice, the existence of protein intolerance in patients with uncompensated liver cirrhosis should be determined based on a history of hepatic encephalopathy and blood ammonia concentration. When patients exhibit protein intolerance, they are given a low protein diet (approximately 0.5–1.0 g/kg/day) with enteral nutrition products for liver failure. However, when patients consume adequate amounts of a well-balanced diet and ammonia concentration does not increase, it is possible to control their condition with granular products. However, when patients cannot achieve an adequate dietary intake, it is recommended that enteral nutrition products should be used in order to improve nutritional status, even if these patients do not have a history of encephalopathy.

Keywords: Branched-chain amino acid (BCAA) preparations; Elemental nutrition products for liver cirrhosis; BCAA granular products

1. Types of nutritional preparations

In Japan, oral branched-chain amino acid (BCAA) preparations are used in nutritional therapy for correcting disorders of protein and amino acid metabolism in patients with liver cirrhosis. There are two forms of oral BCAA preparations: enteral nutrition products for liver failure (or elemental nutrition products for liver cirrhosis) and oral BCAA granular products.

All enteral nutrition products for liver failure (hereafter, enteral nutrition products) are rich in BCAAs: valine (Val), leucine (Leu) and isoleucine (Ile). In a regular dose (2–3 packages/day), 11–17 g of BCAAs can be administered. These products are indicated for treating hepatic encephalopathy in patients with uncompensated liver cirrhosis. However, as these products contain the three major nutrients (protein, sugar and fat), vitamins, minerals, etc., they are administered to improve the nutritional status as well as to improve hepatic encephalopathy [1].

Oral BCAA granular products (hereafter, granular products) are solely composed of BCAAs, and the composition ratio of Val, Leu and Ile is 1:2:1.2. Granular products are indicated for treating malnutrition with hypoalbuminemia in patients with uncompensated liver cirrhosis in whom hepatic encephalopathy has not developed. Patients who are given granular products should be able to consume an adequate diet.

Eight-week administration of granular products improves and increases serum albumin concentration [2]. This results in an improvement of symptoms such as edema in the upper and lower extremities, general fatigue, fatigability and muscular spasm. Therefore, the administration of granular products improves the QOL of patients with liver cirrhosis [3]. It has also been reported that this administration decreases the occur-

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Table 1
Disorders of protein and amino acid metabolism in patients with liver cirrhosis

Decreased protein synthesis and increased catabolism
Malnutrition
Decreased muscle mass
Negative nitrogen balance
Hypoalbuminemia
Decreased urea synthesis
Hyperammonemia
Protein intolerance
Plasma free amino acid inbalance
Decreased branched-chain amino acids (BCAAs)
Increased aromatic amino acids (AAAs)
Increased methionine (Met)

rence frequency of hepatic encephalopathy and increases the mortality of these patients [4].

2. Purposes of the administration of nutritional preparations

Abnormal metabolism of various nutrients is observed in patients with liver cirrhosis. Among them, disorders of protein and amino acid metabolism are the most significant. Disorders of protein and amino acid metabolism in patients with liver cirrhosis are shown in Table 1. Patients with liver cirrhosis have disorders of amino acids in serum. Especially, these patients are characterized by decreased BCAAs and increased aromatic amino acids (tyrosine and phenylalanine) and methionine. Disorders of protein metabolism in patients with liver cirrhosis include hypoproteinemia and hypoalbuminemia. However, protein catabolism increases in peripheral organs such as muscles, and the nitrogen balance is negative. There is a positive correlation between serum albumin concentration and Fischer's ratio, and disorders of protein and amino acid metabolism are simultaneously observed. These disorders are prominent in patients with uncompensated liver cirrhosis, but they are sometimes observed in patients with chronic hepatitis and patients with compensated liver cirrhosis. Therefore, it is assumed that the pathophysiological condition of liver cirrhosis is caused by BCAA deficiency [2]. Additionally, in patients with liver cirrhosis, urea nitrogen synthesis decreases, and excessive protein intake causes hyperammonemia and hepatic encephalopathy. This condition is protein intolerance. Diet therapy is a basic therapy for improving malnutrition and metabolic disorders in patients with liver cirrhosis, but there is a risk that protein intake will deteriorate the pathophysiological condition of protein intolerant patients.

An evaluation was conducted to assess which foods are rich in BCAAs and are suitable for protein intolerance [5]. However, the BCAA content does not differ largely between various types of foods. Therefore, as it is impossible to consume sufficient quantities of BCAAs from foods to correct disorders of protein and amino acid metabolism, oral BCAA preparations were developed.

Disorders of protein and amino acid metabolism deteriorate as the pathophysiological condition advances. We evaluated differences in disorders of protein and amino acid metabolism in outpatients with varying severities of liver cirrhosis. The result of this evaluation is shown in Figs. 1–3.

For each severity, we evaluated the differences in serum total bilirubin concentration, serum albumin concentration and prothrombin time, which are among the parameters of the Child-Pugh classification. Each parameter significantly deteriorated as the severity advanced (Fig. 1). A comparison of acute phase protein (prealbumin, retinol binding protein and transferrin) concentrations, which are used as indicators of visceral protein nutritional status, revealed that these concentrations also decreased as the severity advanced (Fig. 2). The branched-chain amino acids to tyrosine ratio (BTR) was used to evaluate differences in plasma free amino acid concentrations. The result of this evaluation showed that decreased BCAA concentration was observed even in

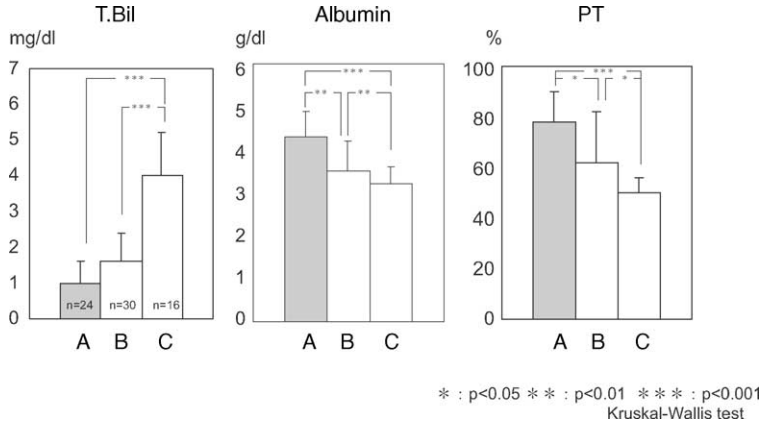

Fig. 1. Differences in the total bilirubin concentration, serum albumin and prothrombin time for each severity of hepatic functions. Seventy patients with liver cirrhosis were divided by Child-Pugh classification. Each parameter of Child-Pugh classification significantly deteriorated as the severity advanced. T.Bil: total bilirubin, albumin: serum albumin, PT: prothrombin time.

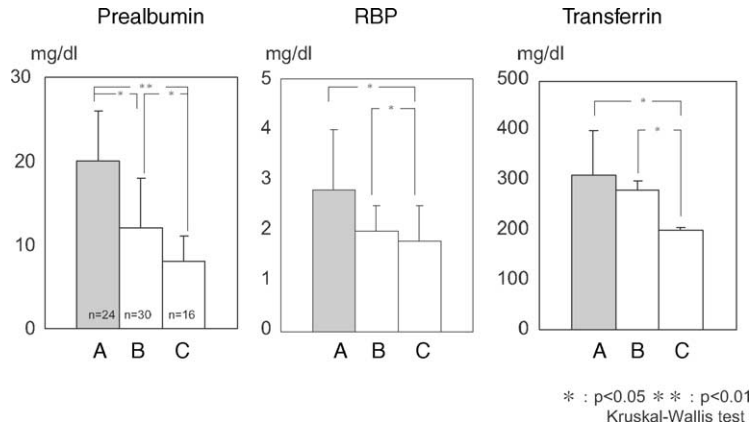

Fig. 2. Differences in the acute phase protein (prealbumin, retinol binding protein and transferrin) concentrations for each severity of hepatic functions. Seventy patients with liver cirrhosis were divided by Child-Pugh classification. Acute phase protein significantly detoiorated as the severity advanced. RBP: retinol binding protein.

grade A, which is less severe, and that BCAA concentration decreases even in patients with compensated liver cirrhosis. On the other hand, tyrosine (Tyr) concentration increases as the severity advances, and as a result, BTR decreases as the severity advances (Fig. 3). Consequently, in patients with liver cirrhosis, it is assumed that disorders of protein and amino acid metabolism progress simultaneously, and that improving disorders of amino acid metabolism plays an important role in improving disorders of protein metabolism.

3. Purpose and effect of BCAA supplementation for patients with liver cirrhosis

As previously mentioned, patients with liver cirrhosis have a characteristic misbalance of serum amino acids as well as malnutrition such as hypoalbuminemia. Conventional diet therapy [6,7] is not sufficient to improve this misbalance, so nutritional therapy, which is also designed for preventing hepatic encephalopathy, is required. Therefore, enteral nutrition products, which are rich in BCAAs, were developed in order to provide each nutrient in a balanced ratio, as well as to supply sufficient quantities of BCAAs.

In Japan, a nationwide survey [8,9] showed that the administration of enteral nutrition products, which are rich in BCAAs, improves malnutrition caused by disorders of amino acid and protein metabolism, such as nitrogen misbalance, hypoalbuminemia and decreased muscular protein, and that this administration also decreases consumed amounts of plasma protein products. It has been reported that long-term administration of these products increases mortality as well as performance status [10].

It has been demonstrated that the administration of BCAA granular products improves nutritional status, including serum albumin concentration, and also increases the cumulative survival rate [3]. Since the administration of BCAA granular products not only improves hypoalbuminemia, but also extends prognosis, we expect that the nutritional effects of BCAA preparations will be evaluated in the near future.

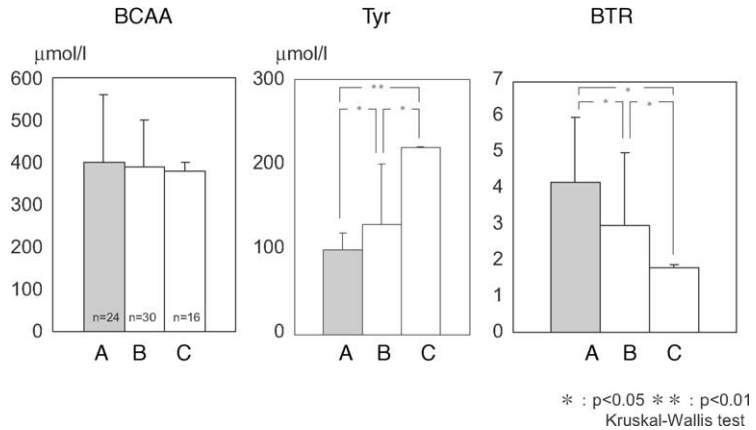

Fig. 3. Differences in the serum free amino acid concentration for each severity of hepatic functions. Seventy patients with liver cirrhosis were divided by Child-Pugh classification. Tyrosine and BTR significantly deteriorated as the severity advanced. Tyr: tyrosine concentration, BTR: branched-chain amino acids to tyrosine ratio.

A recent study by Marchesini et al. [11] showed that the occurrence frequency of adverse events and the quality of life (QOL) of patients who were given BCAA preparations orally for 1 year improved in comparison to the control group, who were given lactalbumin or maltose dextrin.

4. Factors affecting the effect of BCAAs

Since oral BCAA preparations have no effect on some patients, when the administration of these preparations is started, it is necessary to recognize factors, which affect the effect of BCAAs and to take measures against these factors. It goes without saying that compliance is a factor, which affects clinical effects. Other factors include the severity of liver damage and the extent of hepatitis. The relation between the severity of liver damage and clinical effects is shown in Fig. 4. For patients who were given granular products, we evaluated the increase in serum albumin concentration (Δ albumin, g/dl) 3 months after the start of the administration. The serum albumin concentration increased in the grade A patients and the grade B patients, but the administration of granular products had no evident effect on the grade C patients. Therefore, the severity of liver damage is a factor that affects the effect of BCAA preparations, and the administration of oral BCAA preparations has limited clinical effect in grade C patients, in whom the pathophysiological condition has advanced.

Additionally, we divided the patients who were given granular products into two groups: one group in which serum transaminase concentration changed by 100 IU/l or more (the major change group), and the other group in which this concentration changed by less than 100 IU/l (the small change group). We evaluated the increase in serum albumin concentration in these two groups (Δ albumin, g/dl) (Fig. 5). The serum albumin concentration increased in the small change group, but there was no evident increase in the major change group. Therefore, the extent of the hepatitis is also a factor that affects the effect of oral BCAA preparations, and it is necessary to stabilize the change in serum transaminase concentration before starting administration.

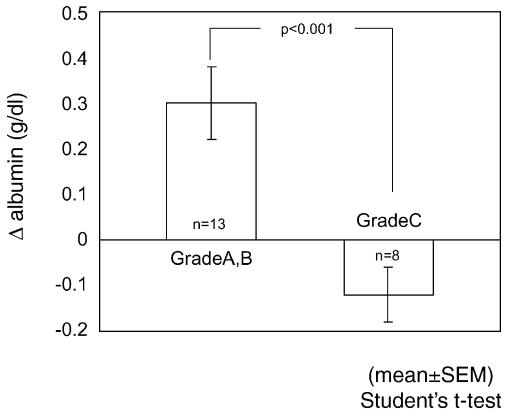

Fig. 4. Clinical effect of BCAA granular products in each severity of liver damage. The serum albumin concentration increased in the grade A patients and the grade B patients, but there was no effect on the grade C patients. Δ Albumin: the increase in serum albumin concentration.

5. Practical method of administering BCAA preparations

5.1. When to start using BCAA preparations

Oral BCAA preparations are indicated for uncompensated liver cirrhosis. However, because the clinical effect of BCAA preparations depends on the severity of liver damage, early diagnosis of uncompensated liver cirrhosis is important. Diagnosis of uncompensated liver cirrhosis is made based on clinical symptoms such as jaundice, edema and peritoneal effusion, and also based on the occurrence of hepatic encephalopathy and intestinal bleeding, including bleeding from esophageal varices. It is easy to diagnose uncompensated liver cirrhosis when patients have clinically evident jaundice, but it is difficult to make a diagnosis when patients do not have jaundice. Based on the existence of edema and/or ascites, we divided patients with liver cirrhosis into the uncompensated liver cirrhosis group and the compensated liver cirrhosis group. We conducted a between-group comparison of biochemical test results (total bilirubin concentration, serum albumin concentration, prothrombin activity, platelet count, serum total protein concentration and serum cholesterol concentration) (Fig. 6). The result of this comparison suggested that indicators of uncompensated liver cirrhosis are (1) serum albumin concentration is 3.5 g/dl or less, (2) prothrombin activity

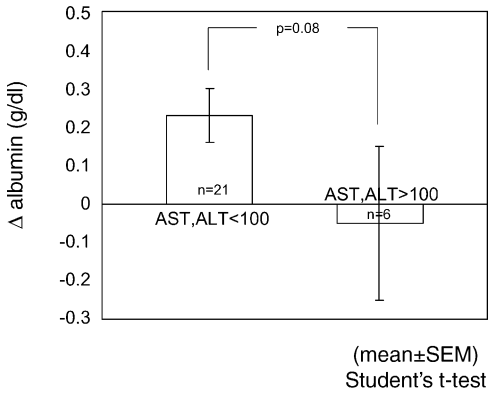

Fig. 5. Clinical effects of BCAA granular products in serum transaminase concentration the patients were divided into two groups: one group in which serum transaminase concentration changed by 100 IU/l or more (the major change group), and the other group in which this concentration changed by less than 100 IU/l (the small change group). The serum albumin concentration increased in the small change group, but there was no evident increase in the major change group. Δ Albumin: the increase in serum albumin concentration.

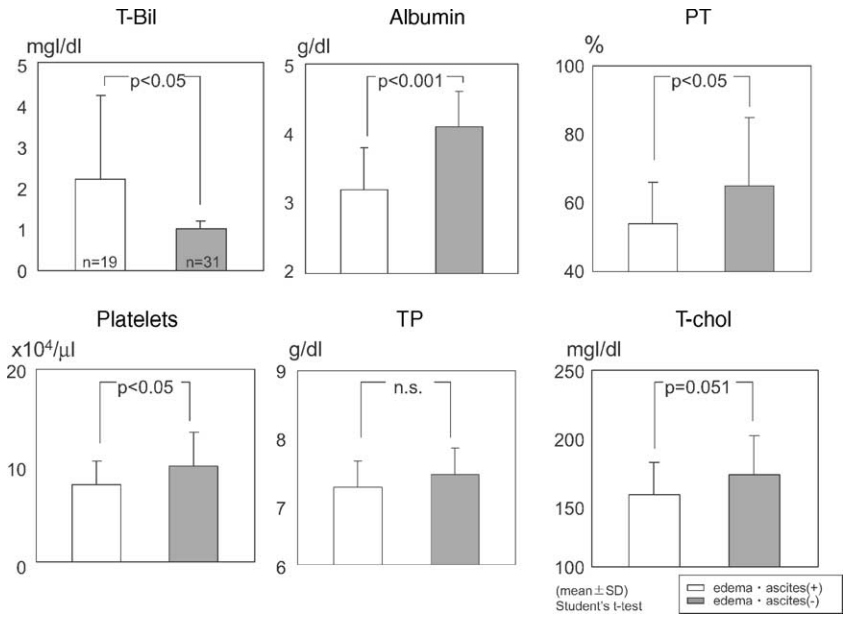

Fig. 6. Biochemical test results of the patients with uncompensated liver cirrhosis. Based on the existence of edema and/or ascites, patients with liver cirrhosis were divided into the uncompensated liver cirrhosis group and the compensated liver cirrhosis group. The indicators of uncompensated liver cirrhosis are: (1) serum albumin concentration is 3.5 g/dl or less, (2) prothrombin activity is 60% or less, and (3) platelet count is 100,000/μl or less. T.Bil: total bilirubin, albumin: serum albumin, PT: prothrombin time, TP: total protein, T-chol: total cholesterol.

is 60% or less, and (3) platelet count is 100,000/μl or less. When these indicators are observed in patients, the administration of oral BCAA preparations should be considered.

5.2. How to select BCAA preparations

Granular products are indicated for patients with uncompensated liver cirrhosis who have no dietary restriction and hypoproteinemia. On the other hand, enteral nutrition products are indicated for patients who have a history of hepatic encephalopathy and exhibit protein intolerance. Therefore, as the targets of granular products and enteral nutrition products are different, it is necessary to exercise caution when selecting BCAA preparations.

In clinical practice, the existence of protein intolerance in patients with uncompensated liver cirrhosis should be determined based on a history of hepatic encephalopathy and blood ammonia concentration. When patients exhibit protein intolerance, they are given a low protein diet (approximately 0.5–1.0 g/kg/day) with enteral nutrition products for liver failure. However, when patients consume adequate amounts of a well-balanced diet and ammonia concentration does not increase, it is possible to control their condition with granular products.

For patients with no history of hepatic encephalopathy, the administration of granular products is started when serum albumin concentration is 3.5 g/dl or less, or when plasma BCAA concentration is low (BTR: 3.5 or less). However, when patients cannot achieve an adequate dietary intake, it is recommended that enteral nutrition products should be used in order to improve nutritional status, even if these patients do not have a history of encephalopathy. For patients with compensated liver cirrhosis who have no clinical symptoms and normal nutritional status, it is important to correct nutritional intake with a well-balanced diet [12]. Therefore, when patients do not have an adequate diet, proper instruction is required.

Additionally, granular products are sometimes used when patients complicated with diabetes mellitus require caloric restriction, or when water restriction is required. When encephalopathy occurs during the administration of granular products, protein restriction and the administration of enteral nutrition products are required in order to improve this pathophysiological condition [12]. In all cases, diet therapy is the basic treatment for malnutrition and metabolic disorders in patients with liver cirrhosis. Understanding each patient's dietary intake and attempting to provide dietary instructions are key points to increasing the effect of therapy with oral BCAA preparations.

5.3. Effects of concomitant administration of BCAA preparations

The method of selecting oral BCAA preparations, which include enteral nutrition products and granular products, was previously described. However, it is unclear whether a dose of BCAAs is optimal for each patient.

We attempted to concomitantly administer enteral nutrition products and granular products to eight patients with liver cirrhosis (five males, three females). Liver cirrhosis was caused by virus in five of the patients, alcohol intake in two

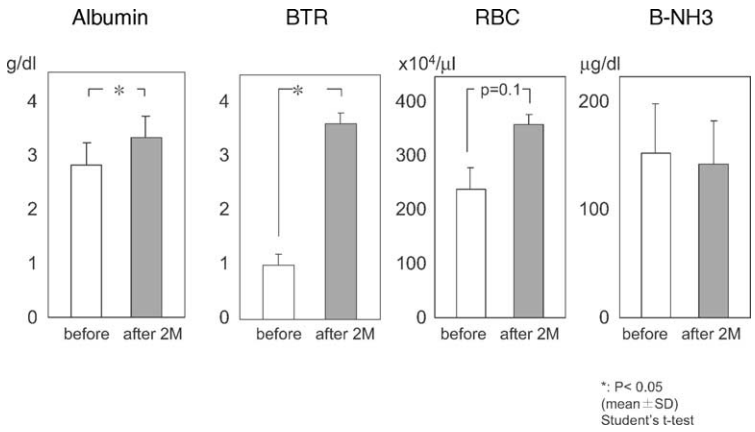

Fig. 7. Concomitant administration of BCAA granules and enteral nutrition products for liver failure. There were increases in the serum albumin concentration, branched-chain amino acids to tyrosine ratio (BTR), red blood cell count and decreases the blood ammonia concentration. Albumin: serum albumin, BTR: branched-chain amino acids to tyrosine ratio, RBC: red blood cell count, B-NH_3: blood ammonia concentration, before: before addition of BCAA preparations, after 2M: 2 months after addition of BCAA preparations.

of the patients and PBC in one of the patients. The severity (Child-Pugh classification) was grade A in two of the patients, grade B in five of the patients and grade C in one of the patients.

The concomitant administration was started because in two of the patients, hypoproteinemia persisted during the administration of enteral nutrition products, in four of the patients, hypoproteinemia persisted during the administration of BCAA granules, and in two of the patients, hepatic encephalopathy occurred during the administration of BCAA granules. Since increasing doses of BCAA granules or enteral nutrition products is restricted by health insurance, concomitant administration was attempted for these patients. On average, the dose of BCAA granules increased from 12 to 18 g after the concomitant administration (Fig. 7).

An evaluation on the result of laboratory tests performed 2 months after the start of the concomitant administration showed that there were increases in the serum albumin concentration, branched-chain amino acids to tyrosine ratio (BTR), red blood cell count and hemoglobin level. On the contrary, the concomitant administration reduced the blood ammonia concentration. Consequently, it might be effective to increase the dose of BCAA granules with concomitant use of other preparations when the regular dose of oral BCAA preparations cannot increase serum albumin concentration, or when hepatic encephalopathy occurs. Additionally, we consider that a future task is to determine an optimal dose of BCAA preparations in each case and to establish a regimen that includes this optimal dose.

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