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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

The efficacy of nocturnal administration of branched-chain amino acid granules to improve quality of life in patients with cirrhosis

Hisashi Hidaka · Takahide Nakazawa · Shinji Kutsukake · Yoshiki Yamazaki · Izumi Aoki · Shiro Nakano · Noriyuki Asaba · Tsutomu Minamino · Juichi Takada · Yoshiaki Tanaka · Yusuke Okuwaki · Masaaki Watanabe · Akitaka Shibuya · Wasaburo Koizumi

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Abstract
Background Nocturnal administration of branched-chain amino acid (BCAA) granules improves serum albumin levels in patients with cirrhosis. However, it is unclear whether or not this administration method can improve the patients' quality of life (QOL). In this study, we aimed to investigate the efficacy of BCAA granules, given nocturnally, in improving QOL in these patients.
Methods We performed a multicenter, randomized controlled trial examining the comparative effects of BCAA granules given orally for 3 months with daytime or nocturnal administration in patients with compensated cirrhosis. Health-related QOL was measured by a Japanese version of the questionnaire on subjective and objective symptoms, and the Short Form-8 (SF-8) questionnaire.
Results Twenty-one patients received BCAA granules three times a day (one sachet after each meal: the daytime group), and 16 patients received the granules twice a day (one sachet after breakfast, and two sachets before bedtime: the nocturnal group). Baseline characteristics did not differ between the groups (whole cohort: Child-Pugh grade A/B, 21/16; mean age, 68.2 years). There was no significant difference in any of the subjects revealed by the questionnaire regarding subjective or objective symptoms, or by the SF-8 between the daytime group and the nocturnal group after 3 months of treatment. The daytime group showed a significant effect on general health, vitality, social functioning, mental health, and role emotional as revealed on the SF-8. Conversely, the nocturnal group exhibited a significant decrease in the occurrence of muscle cramps in the legs ($P = 0.014$) and significantly improved Fisher's ratio after 3 months ($P = 0.04$).
Conclusions Nocturnal administration of BCAA granules in patients with cirrhosis reduced the occurrence of muscle cramps in the leg but did not improve the patients' QOL.

Keywords Liver cirrhosis · Branched-chain amino acid · Quality of life

The trial described in this work has been registered under the following trial number: UMIN 000005274.

H. Hidaka (✉) · T. Nakazawa · T. Minamino · J. Takada · Y. Tanaka · Y. Okuwaki · M. Watanabe · A. Shibuya · W. Koizumi
Department of Gastroenterology,
Kitasato University School of Medicine,
2-1-1 Asamizodai, Minami, Sagamihara,
Kanagawa 252-0380, Japan
e-mail: hisashi7@kitasato-u.ac.jp

S. Kutsukake
Kutsukake Clinic, Sagamihara, Japan

Y. Yamazaki
Hiratsuka Kyosai Hospital, Hiratsuka, Japan

I. Aoki
Toshiba Rinkan Hospital, Sagamihara, Japan

S. Nakano
Kakunaka Clinic, Sagamihara, Japan

N. Asaba
ASABA Clinic, Sagamihara, Japan

Abbreviations

AAA	Aromatic amino acid
BCAA	Branched-chain amino acid
CT	Computed tomography
HCC	Hepatocellular carcinoma
LES	Late evening snack
OGTT	Oral glucose tolerance test
PEM	Protein-energy malnutrition

QOL Quality of life
SF-8 Short Form-8

Introduction

It has been reported that nutritional state influences survival in patients with liver cirrhosis [1]. The energy balance in patients with liver cirrhosis is characterized as protein-energy malnutrition (PEM), disorder of glycolysis, decline of glycogenosis, negative nitrogen balance, and hyperlipolysis [2–4]. Patients with advanced liver cirrhosis show a characteristic decrease in the plasma concentration of branched-chain amino acids (BCAAs) and an increase in aromatic amino acids (AAAs). Two large randomized trials have shown that the long-term administration of BCAA supplements decreased the progression of hepatic failure and was associated with improved survival in patients with cirrhosis [5, 6]. Moreover, nocturnal energy supplementation improved nitrogen balance and abnormal fuel metabolism in patients with cirrhosis [7–9]. As an intervention for energy malnutrition, frequent meals or a late evening snack (LES) have been recommended [7–11]. The group of Sakaida et al. (Okamototo et al. [12], Sakaida et al. [13], and Tsuchiya et al. [14]) showed that 1-week administration of a BCAA-enriched nutrient, Aminoleban EN® (Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan) (210 kcal) in hospitalized patients with liver cirrhosis improved energy malnutrition, but glucose intolerance occurred 12–14. Of note, long-term use of LES for 3 months showed worsened glucose tolerance, as assessed with the 75- oral glucose tolerance test (OGTT) [15]. Fukushima et al. [16] revealed in their study that nocturnal administration of BCAA granules, giving one sachet (L-isoleucine 952 mg, L-leucine 1904 mg, L-valine 1144 mg) after breakfast and two sachets before bedtime, improved the serum albumin level in cirrhotic patients who had shown no improvement in serum albumin level with daytime BCAA administration (given with each meal). However, it is unclear whether the method of BCAA administration can improve quality of life (QOL) in patients with cirrhosis. The objective of this study was to investigate the efficacy of nocturnal administration of BCAA granules in improving QOL in patients with cirrhosis.

Patients and methods

Study design and selection of patients

Between October 2008 and September 2010, this randomized controlled study was conducted in 9 hospitals and 4 medical clinics in Japan. The protocol was undertaken with the approval of the Institutional Review Board of each participating institution and in accordance with the World Medical Association's Declaration of Helsinki (1989). The final protocol was approved by the Ethics Committee of the Kitasato University, Sagamihara, Japan (C-Ethics Committee, ID 08-438). Written informed consent was obtained from each enrolled subject. The trial described in this work has been registered under the following trial number: http://www.umin.ac.jp/ctr/index.htm, UMIN 000005274.

The inclusion criteria were patients with cirrhosis who were aged between 20 and 80 years whose serum albumin level ranged from 3.1 to 3.5 g/dl. Cirrhosis was diagnosed on the basis of clinical, radiological, and laboratory parameters, and/or liver biopsy. The patients underwent endoscopy and computed tomography (CT). Exclusion criteria were: (1) Child-Pugh score $\geq$10; (2) hepatocellular carcinoma (HCC); (3) endoscopically confirmed existing moderate or large varices and post-ligated ulcers 1 month after final esophageal variceal ligation; (4) ongoing pharmacological therapy for portal hypertension with nonselective beta-blockers, nitrates, and angiotensin II type 1 receptor blockers; (5) portal thrombosis; (6) drinking alcohol within 3 months before the start of the study; (7) a history of BCAA supplementation in the previous 3 months; (8) pregnancy; and (9) allergy or past adverse reaction to BCAA.

Instruments for QOL assessment

A disease-specific health-related quality of life (HRQOL) analysis and a cross-sectional analysis of general HRQOL were conducted using the Japanese version of questionnaires on subjective and objective symptoms in patients with liver cirrhosis, and using the Japanese version of the Medical Outcomes Study 8-Item Short-Form Health Survey (SF-8). The validity and reliability of the Japanese versions of both questionnaires have already been confirmed, as described previously [17]. The Japanese version of the questionnaires on subjective and objective symptoms comprises 6 subscales (sluggishness, fatigue, general itching, anorexia, abdominal fullness, and muscle cramps). The SF-8 comprises 8 subscales (GH, general health; PF, physical functioning; RP, role limitation due to physical problems; BP, body pain; VT, vitality; SF, social functioning; MH, mental health; RE, role limitation due to emotional problems), and all of these categories are compatible with those in the SF-8. In the present study, the score of each of the 8 subscales, the physical health component summary score (PCS), and the mental health component summary score (MCS) were measured using the norm-based scoring method, which was based on a large-scale population study conducted in Japan [17]. QOL

scores are shown as mean scores with a 95 % confidence interval (95 % CI), with the higher scores representing better QOL. In order to enhance the potential for unbiased and truthful answers, participants responded anonymously to all questions and returned the questionnaires using return stamped-addressed envelopes.

Intervention protocol

Baseline evaluation included physical examination and routine laboratory tests. Daily food intake was estimated by a self-administered questionnaire. Screening information of possibly eligible patients was transmitted to the registration center. After confirmation of eligibility, the patients were randomly assigned in a 1:1 ratio by the center to either daytime BCAA granule administration [4 g BCAA (Livact® Granules; Ajinomoto Pharmaceutical, Tokyo, Japan): L-isoleucine 952 mg, L-leucine 1904 mg, L-valine 1144 mg] after each meal, or nocturnal BCAA granule administration (4 g after breakfast and 8 g before bedtime) for 3 months. Study randomization was conducted by computer to achieve a balance between the two groups without stratification. Daily food intake was mandated by the patients' physicians in charge at 30 kcal/kg/day and 1.2 g protein/kg/day. We assessed compliance with treatment at each outpatient visit by interview.

Follow up

The initial clinical visit was 2 weeks after the introduction of treatment in both arms, with a clinical visit again after another 2 weeks. The follow-up interval was every 4 weeks. Biochemical (serum albumin, aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin, free fatty acid, cholinesterase, NH3, glycated albumin, and Fisher's ratio) and hematological profiles (platelets and prothrombin time) were obtained at each consultation after the patients had had an overnight fast. After 3 months of treatment, a clinical examination was performed, and patients underwent CT examinations as part of the HCC surveillance. Adverse events arising from BCAA granule administration were defined according to the Common Terminology Criteria for Adverse Events version 3.0 or 4.0. After recruitment of the last patient, follow up was designed to be continued in both treatment arms for 3 months.

Sample size calculation and statistical analysis

To our knowledge, only one study in the literature has investigated the effect of nocturnal BCAA granule administration in patients with cirrhosis [16]. In that study, nocturnal BCAA administration improved protein metabolism, but its effect on QOL was not examined [16]. Therefore, in the present study, we calculated the sample size by estimating improvement in the serum albumin level. We estimated that the rate of improvement after 3 months of treatment would be not <50 % in the nocturnal group and at least 10 % in the daytime group. At least a 10 % failure rate in both groups was estimated previously. On the basis of a 40 % difference in the improvement rate after 3 months of follow up, a sample size of 10 patients per group would provide 80 % power with a 2-sided alpha of 0.05 by log-rank test.

Values for continuous variables are presented as means ± standard deviation (SD) or medians (ranges). The paired or non-paired Student's *t*-test was used to assess the significance of differences in the comparison of normally distributed data, and the Mann–Whitney *U*-test or the Wilcoxon test was used for the non-normally distributed data, while numerical variables were assessed by Pearson's χ^2test or Fisher's exact test, as appropriate. *P* values of <0.05 were considered to indicate statistical significance. All reported *P* values were two-sided. Analyses were performed using SPSS version 17.0 software (SPSS, Chicago, IL, USA).

Results

Between September 2008 and August 2010, total of 50 patients with liver cirrhosis were refferred for possible randomization after screening from 4 hospitals and 2 clinics of the 13 centers open to the study (Fig. 1). In all, 10 patients were excluded from randomization: 7 patients who had previously received BCAA administration, and 3 patients who were confirmed to have HCC. Forty patients were initially enrolled and randomized. However, after randomization, 3 patients in the nocturnal group opted for other treatments because their regular pharmacy could not keep up our treatment schedule with nocturnal BCAA granule administration. Therefore, 21 patients received BCAA granules three times a day (one sachet after each meal: the daytime group), and 16 patients received the BCAA granules twice a day (one sachet after breakfast and two sachets before bedtime: the nocturnal group). The contributions from the six centers were as follows: Kitasato University East Hospital, $n = 23$; Kitasato University Hospital, $n = 2$; Kutsukake Clinic, $n = 7$; Hiratsuka Kyosai Hospital, $n = 3$; Toshiba Rinkan Hospital, $n = 1$; Kakunaka Clinic, $n = 1$.

Baseline characteristics did not differ between the groups. The main characteristics of the patients are summarized in Table 1. There were no significant differences between patients randomized to the daytime group and those in the nocturnal group in any of the parameters.

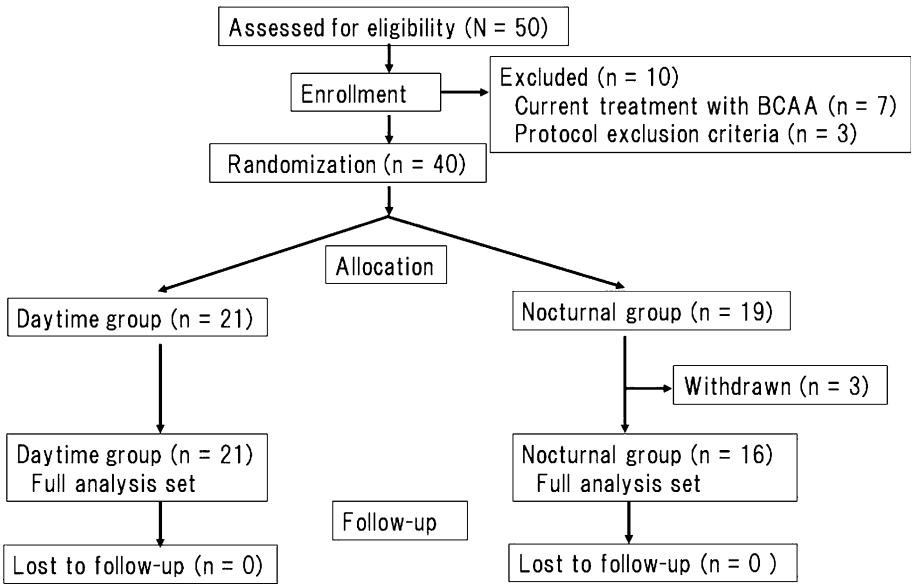

Fig. 1 Flow diagram of study recruitment through follow up. *BCAA* branched-chain amino acid

Table 1 Patients' baseline clinical and biochemical characteristics

Patients	Daytime group $n = 21$	Nocturnal group $n = 16$	P
Age (years)	73 (41–83)	72 (52–79)	0.70
Gender (male/female)	8/13	7/9	0.78
Etiology			0.24
Alcohol	1	2	
HBV	1	1	
HCV	16	7	
Others	3	6	
Liver function			
Child-Pugh class (A/B)	12/9	9/7	0.96
BMI (kg/m^2)	22.2 (14.9–30.3)	23.9 (19.2–29.2)	0.21
Ascites (yes/no)	0/21	0/16	
History of HCC therapy (yes/no)	4/17	4/12	0.16

Values for age and BMI are expressed as medians and ranges

HBV hepatitis B virus, *HCV* hepatitis C virus, *BMI* body mass index

QOL assessment

The therapy was well accepted and tolerated. There were no significant differences in any of the subjects according to the results of the questionnaire survey on either subjective or objective symptoms, or on the SF-8 between the daytime group and the nocturnal group after 3 months of treatment.

All the patients had a significant decrease in the occurrence of muscle cramps in the legs ($P = 0.004$) (Fig. 2a) and all exhibited significant effects on general health scores as revealed by the SF-8 after 3 months ($P = 0.01$) (Fig. 3a). After 3 months of treatment, the daytime group had a decrease in the occurrence of muscle cramps in the legs (Fig. 2b), and exhibited significant effects on general health ($P = 0.005$), vitality ($P = 0.049$), social functioning ($P = 0.016$), mental health ($P = 0.037$), and role emotional ($P = 0.029$) as revealed by the SF-8 (Fig. 3b). On the other hand, although the nocturnal group had a significant decrease in muscle cramps in the legs ($P = 0.014$) (Fig. 2c), there were no significant effects on any parameter of the SF8 in this group (Fig. 3c).

Changes in laboratory data

After 3 months' treatment, there were no significant differences in any laboratory parameters between the daytime group and the nocturnal group. After 3 months, Fisher's ratio was significantly increased in the nocturnal group (1.48 ± 0.04 vs. 2.32 ± 0.71, $P = 0.04$) compared with the value in the daytime group (1.42 ± 0.24 vs.

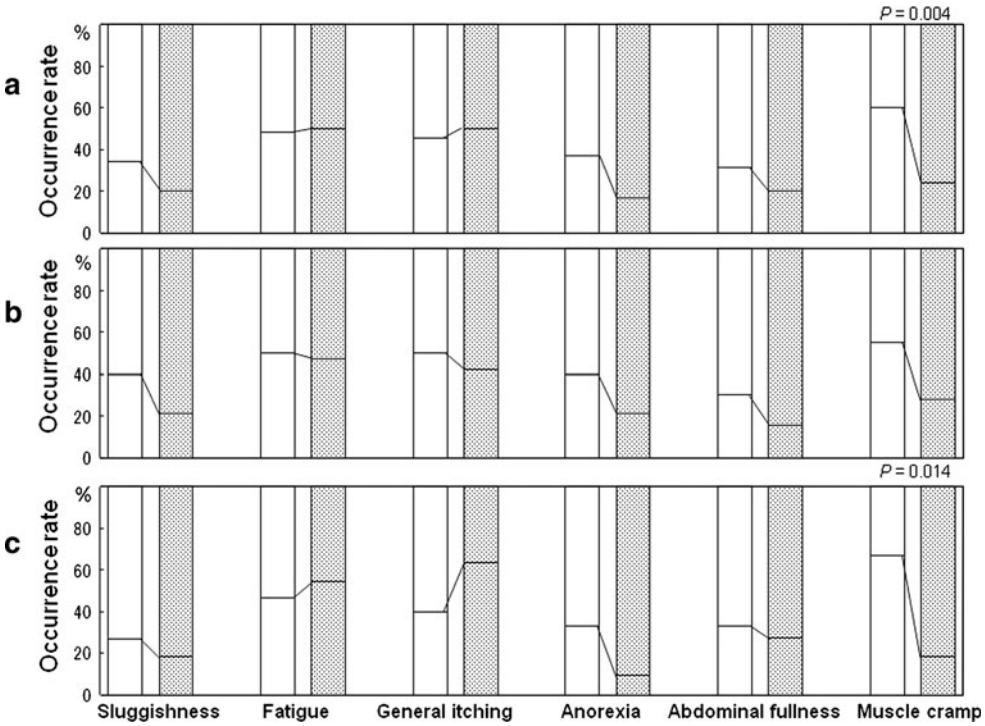

Fig. 2 Occurrence rates from the Japanese version of questionnaires on subjective and objective symptoms in patients with liver cirrhosis. All the patients had a significant decrease in the occurrence of muscle cramps in the legs ($P = 0.004$) (nocturnal group, $P = 0.014$). *White bars*, pretreatment; *dotted bars*, after 3 months of treatment. **a** All the patients, **b** daytime group, **c** nocturnal group

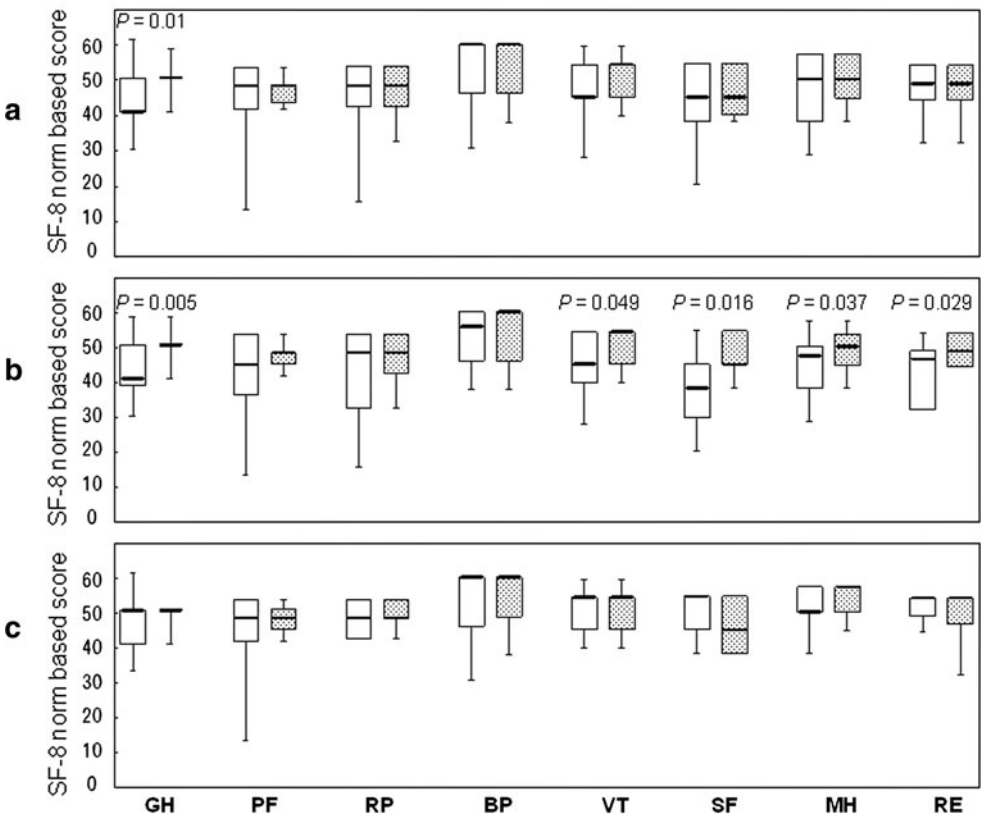

Fig. 3 Results from the Japanese version of the Medical Outcomes Study Short-Form 8-Item Health Survey (SF-8). All the patients showed a significant effect revealed by the general health scores on the SF-8 ($P = 0.01$). The daytime group showed a significant effect on general health ($P = 0.005$), vitality ($P = 0.049$), social functioning ($P = 0.016$), mental health ($P = 0.037$), and role emotional ($P = 0.029$) as revealed on the SF-8. Conversely, the nocturnal group did not show any significant effects on any parameters of the SF8. *GH* general health, *PF* physical functioning, *RP* role limitation due to physical problems, *BP* body pain, *VT* vitality, *SF* social functioning, *MH* mental health, *RE* role limitation due to emotional problems. *White bars*, pretreatment; *dotted bars*, after 3 months of treatment. **a** All the patients, **b** daytime group, **c** nocturnal group

1.75 ± 0.16, $P = 0.18$). However, serum albumin after 3 months was not changed in either group (3.34 ± 0.15 vs. 3.42 ± 0.19 g/dl, $P = 0.85$ in the nocturnal group, and 3.35 ± 0.18 vs. 3.40 ± 0.35 g/dl, $P = 0.59$ in the daytime group) (Table 2). Moreover, glycated albumin was not changed by BCAA administration.

Table 2 Changes in chemical markers in the daytime and nocturnal groups

	Daytime group			Nocturnal group		
	Baseline	3 Months	*P*	Baseline	3 Months	*P*
Albumin (g/dl)	3.4 (3.1–3.8)	3.4 (3.0–4.0)	0.59	3.4 (3.1–3.5)	3.4 (3.0–3.8)	0.85
Platelets ($\times 10^4$/μl)	6.8 (3.8–38.4)	7.35 (3.3–16.6)	0.17	7.95 (4.0–12.8)	9.05 (4.4–18.7)	0.46
AST (IU/l)	65 (24–139)	72 (26–149)	0.28	60 (21–139)	53 (31–115)	0.99
ALT (IU/l)	42 (11–105)	49 (17–123)	0.32	41 (14–112)	32 (17–96)	0.57
T. Bil. (mg/dl)	1.1 (0.4–2.8)	1.1 (0.4–2.2)	0.46	1.0 (0.5–2.7)	0.9 (0.4–2.8)	0.08
PT (%)	73.5 (58.1–90.9)	76.0 (54.0–87.0)	0.65	63.4 (50.0–81.4)	70.8 (54.5–82.2)	0.32
NH_3 (μg/dl)	70 (19–108)	51 (19–104)	0.33	29 (10–138)	19 (17–158)	0.61
Free fatty acid (Eq/l)	652 (99–2437)	261 (87–2736)	0.83	281 (39–2685)	579 (39–2850)	0.72
Cholinesterase (mg/dl)	144 (59–187)	149 (41–252)	0.59	128 (87–273)	150 (87–246)	0.79
Glycated albumin (%)	21.0 (15.5–44.8)	19.3 (16.6–47.8)	0.91	20.0 (16.0–42.3)	19.5 (16.8–39.4)	0.73
Fisher's ratio	1.27 (1.00–2.23)	1.60 (1.33–2.30)	0.18	1.57 (1.14–1.72)	2.12 (1.15–3.52)	0.04
AFP (ng/ml)	5.65 (3.6–222.0)	9.0 (2.9–59.5)	0.35	11.1 (2.1–432.0)	14.7 (1.8–954.0)	0.36

All data values are expressed in medians and ranges

T. Bil. total bilirubin, *PT* prothrombin time, *AFP* alpha-fetoprotein, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase

Treatment compliance

Overall, 20 (95.2 %) patients in the daytime group and 15 (93.8 %) patients in the nocturnal group received more than 80 % of the planned daily dose of the study drug.

Adverse reactions

Adverse reactions to BCAA administration were identified in 4 patients in the nocturnal group: 2 patients developed abdominal distension (grade 2), and 2 patients developed general itching (grade 1). However, all 4 patients recovered with conservative treatment.

HCC and esophageal varices

Two patients in each arm of the present study developed HCC after 3 months of follow up. There were no patients who bled from esophageal varices during the observation period.

Discussion

To our knowledge, this is the first multicenter randomized controlled trial to have investigated the efficacy of nocturnal BCAA granule administration in improving QOL in patients with cirrhosis. In this study, the administration of BCAA granules significantly reduced the occurrence of muscle cramps in the leg for all the patients and the nocturnal group. Generally, muscle cramps are caused by a variety of factors, including diuretic treatment, intolerance of amino acids, and deficiency of vitamin E and taurine [18, 19]. Marchesini et al. [6] reported that the frequency of muscle cramps, which was associated with poor QOL in patients with decompensated cirrhosis, was dramatically reduced by BCAA supplementation over a period of 3 months; however, the BCAA supplementation was associated with poor QOL in patients with decompensated cirrhosis. Of note, in our study, QOL in the daytime group was significantly improved after 3 months of treatment compared with that in the nocturnal group. In particular, the components of GH, VT, SF, MH, and RE improved significantly in the daytime group. We could not explain this discrepancy between the QOL findings in our study and those of Marchesini et al. [6]. However, in our nocturnal group, Fisher's ratio, which is the most important index of an amino acid imbalance, was significantly increased compared with that in the daytime group. In the matter of the results of the plasma Fisher's ratio, it is necessary to consider the influence of the interval between the last BCAA intake and blood sampling in the fasting state. In a single-administration study of BCAA in healthy rats, the mean maximum blood concentration of BCAA was observed after about 4 h and the concentration gradually decreased after that, and the mean half-life was about 58 h [20]. However, it is considered that the preservation of a higher BCAA concentration until morning is particularly important in patients with decompensated cirrhosis. Patients with liver cirrhosis cannot constantly maintain the concentration of BCAA administered in the daytime until nighttime because the BCAA is consumed for their

daytime physical activity [16]. We speculated that nocturnal BCAA administration would complement the deficiency experienced during the night. However, we found that nocturnal administration tended to induce more abdominal distension and general itching at night than daytime administration, thus lowering the QOL in nocturnal group.

In the present study, the glycated albumin level was not changed by BCAA administration. Sako et al. [18] reported that the administration of the BCAA supplement, Aminoleban EN® (210 kcal), in the evening decreased the number of muscle cramps in 8 outpatients with advanced liver cirrhosis. However, excess elevation of blood glucose occurs after meals in liver cirrhosis patients [21]. Aoyama et al. [15] reported that patients with a glucose level of more than 200 mg/dl 2 h after a 75-g OGTT experienced impaired glucose tolerance after 3 months' administration of BCAA supplements. However, impaired glucose tolerance did not occur with the administration of BCAA granules that consisted of only 4 g BCAA. A previous clinical trial has reported that BCAA administration decreased plasma glucose levels in patients with advanced liver cirrhosis [22]. Furthermore, Kawaguchi et al. [23] reported that BCAA improved insulin resistance in patients with chronic liver disease. Therefore, it is possible that BCAA granules are more useful for muscle cramps in patients with glucose intolerance than are BCAA supplements. On the other hand, Nakaya et al. [24] reported that BCAA supplements improved the nutrition state (serum albumin, energy metabolism) in patients with decompensated cirrhosis. Accordingly, in decompensated patients who cannot eat enough, it seems to be more feasible for them to take BCAA supplements.

HCC was noted in 2 patients with hepatitis C in each arm of the present study after 3 months of treatment with BCAA granules. It seems that the HCC occurrence rate (11.1 % per 3 months) in this study was much higher than the general rate (2–5 %) in Japan [25]. All 4 patients for whom HCC was noted had received HCC therapy previously, and their serum albumin levels had decreased after 3 months of the BCAA administration. The present study might have been better if we had not included these 4 patients who had previously received HCC therapy. However, a recent clinical study reported that long-term BCAA administration inhibited the development of HCC in liver cirrhosis patients with hepatitis C [5]. Furthermore, one study from Japan showed that BCAA administration in patients with liver cirrhosis suppressed HCC recurrence after treatment with radiofrequency ablation [26]. Further studies are needed to clarify whether or not there are clinical benefits of BCAA administration that would help prevent HCC.

There are three limitations of the present study. First, we could not establish a control group (i.e., a no-treatment group). However, large trials of BCAA supplements show that they decrease the progression of hepatic failure and are associated with improved survival in patients with decompensated cirrhosis [5, 6]. Therefore, we believe that it is not necessary to compare the BCAA administration results with a no-treatment control group. The second limitation is the short-term (3 months) administration. If we had administered BCAA granules for a longer term (e.g., 1 year), the serum albumin level might have increased significantly. On the other hand, the high rate of compliance in our study might have been due to the short-term administration. Finally, after the randomization, 3 patients in the nocturnal group chose early withdrawal because their regular pharmacy could not keep up with our treatment schedule. Accordingly, our study did not follow ITT (intention-to-treat) analyses because we omitted these patients from analysis in this study. However, it is considered that this withdrawal was caused by institutional error and not because of the patients' lack of compliance.

In conclusion, the daytime administration of BCAA granules significantly improved the QOL in patients with cirrhosis. And, while nocturnal administration significantly reduced patients' leg muscle cramps, it did not seem to improve their QOL.

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Conflict of interest H. Hidaka has served as a consultant and speaker for Ajinomoto Pharmaceutical Co., Inc., Tokyo, Japan; all the other authors have no personal interests to disclose in relation to this article.

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