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Effects of branched-chain amino acids supplementation in patients with cirrhosis and a previous episode of hepatic encephalopathy. A randomized study.

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ABSTRACT

OBJECTIVES: The protein intake impacts on nutritional status and may determine the recurrence of hepatic encephalopathy (HE). A low-protein diet has been considered the standard treatment after an episode of HE, while branched-chain amino acids (BCAA) have been shown to improve minimal HE. We performed a study to investigate the long-term effects of supplementing a protein-controlled diet with BCAA.

METHODS: A randomized, double-blind, multicenter study that included 116 patients with cirrhosis and a previous episode of HE was conducted in four tertiary care hospitals. All patients received a standard diet of 35 kcal/kg/d and 0.7 g of proteins/kg/d and a supplement of 30 g of BCAA (BCAA group) or maltodextrin (MDX group) during 56 weeks.

RESULTS: The actuarial risk of remaining free of HE did not differ between both groups (BCAA=47%, MDX=34%, P=0.274), but patients of the BCAA group exhibited a better outcome in two neuropsychological tests and an increase in the mid-arm muscle circumference. Recurrence was associated with low plasma albumin at baseline and a decrease in sodium and an increase in creatinine during follow-up. Patients with recurrence of HE exhibited a lack of improvement in global cognitive function.

CONCLUSIONS: Diet supplementation with BCAA after an episode of HE does not decrease recurrence of HE. However, supplementation with BCAA improves minimal HE and muscle mass. Our results support that prevention of circulatory dysfunction and hyponatremia may be the best approach to avoid recurrence of HE and neuropsychological sequels of repeated episodes of HE.

Word count of abstract: 244 words.

Keywords: Hepatic encephalopathy; proteins of the diet; branched-chain amino acids; liver cirrhosis; nutritional status.

INTRODUCTION

Hepatic encephalopathy (HE) is a major complication of cirrhosis that is associated with bad prognosis, poor quality of life and high risk of recurrence (1,2). Treatment of HE is based on suppression of precipitating factors, reduction of ammonia absorption and nutritional measures (3). Protein malnutrition is common in cirrhosis and correlates to mortality and development of complications (4). However, providing a large amount of proteins increases plasma ammonia and may precipitate HE. The administration of a diet with a low-protein content has been considered the mainstay of treatment and prevention of HE (5). On the other hand, protein restriction has been criticized due to the risks of worsening the nutritional status and lack of supportive studies (6). In a prior clinical trial we demonstrated that a low-protein diet does not improve the outcome of episodic HE (7).

In addition to the amount of proteins, the characteristics of amino acids have also been implicated in the development of HE (8). Patients with advanced cirrhosis exhibit characteristically a decrease in the plasma concentration of branched-chain amino acids (BCAA) and an increase in aromatic amino acids (AAA). It was postulated that the AAA would flood the central nervous system because AAA and BCAA compete for entry by the same transporter (L-system) across the blood–brain barrier (9). Augmented uptake of AAA could result in an imbalance in the synthesis of dopamine, noradrenaline, and serotonin in the brain and may cause the formation of ‘‘false neurotransmitters’’. Neurochemical data have not confirmed the hypothesis, which has become obsolete (10), but a series of studies indicate that in advanced cirrhosis oral supplementation with

BCAA may improve cognitive function (11,12), especially in patients with chronic HE (13).

The mechanism of action of BCAA can be multiple, but the main factor appears to be improvement of nutritional status by inhibiting protein degradation and enhancing protein synthesis (14). The administration of BCAA to patients with cirrhosis induces a positive nitrogen balance and an increase in the concentration of plasma albumin (13,15). Through this mechanism BCAA may increase the mass of muscle tissue. Since muscle is an important site for extrahepatic ammonia detoxification (16), increase of muscle tissue can reduce plasma ammonia (11). In addition, BCAA may have specific effects on liver function; two large randomized trials have generated evidence that oral BCAA slow the progression of advanced cirrhosis and prolong event-free survival (15,17).

In spite of the beneficial effects seen in the above mentioned clinical trials, the current recommendation only includes oral supplementation with BCAA to patients with liver disease who are intolerant to standard protein intake (18). The rationale for this limitation is based on the fact that in the mentioned randomized trials HE was not part of the inclusion criteria. Additionally, the positive effect was difficult to interpret as it was observed on compound end-points, which combine survival, hospitalization and cirrhosis complications. From these results it is not possible to ascertain the role of BCAA in HE, which patients benefit and to what extent (19). For this reason we designed a study to assess whether BCAA supplementation could decrease the recurrence of HE in a well defined population of patients with advanced cirrhosis: those who have

been recently discharged from the hospital after having experienced an episode of HE.

METHODS

Between January 2003 and December 2008, a randomized, double-blind, controlled study was conducted in four tertiary care hospitals. The protocol conformed to the Declaration of Helsinki and Guidelines for Good Clinical Practice in Clinical Trials and was approved by the Institutional Review Boards, in accordance to the Spanish legislation. A written informed consent was obtained from all participants.

Patient selection

Patients were invited to participate in the study if the following features were present: 1) liver cirrhosis; 2) hospitalized for an episode of HE within two months prior to inclusion; 3) age between 18 and 85 years; 4) compliance with a standard diet during two weeks prior to inclusion. Exclusion criteria were: 1) end-stage cirrhosis (MELD score > 25); 2) marked cognitive disorder (Spanish Mini-mental test < 27); 3) non-treatable hepatocarcinoma (beyond Milan criteria); 4) comorbid conditions with life expectancy < 6 months; 5) neurological conditions that difficult assessment of HE (e.g. Parkinson's disease, Alzheimer disease, stroke…); 6) diseases requiring a specific diet.

Nutritional intervention

Prior to randomization, potential participants were evaluated during two weeks for compliance with a standard diet designed and supervised by the same dietician (G.C. or P.G.), who followed the patients during the whole study. This standard diet contained 35 kcal/kg/d and 0.7 g of proteins/kg/d, both adjusted to ideal weight. The diet was divided in 5-6 meals, one of them at late evening.

After ensuring an adequate compliance, patients were randomized to a) BCAA group or b) Maltodextrin (MDX) group. Both groups received the same standard diet and in addition a sachet with 30 g of a white powder that provided 120 kcal. The powder corresponded to BCAA (leucine: 13.5 g, isoleucine: 9 g, valine: 7.5 g) or to MDX, kindly provided by SHS International Ltd. The supplements were administered twice daily mixed with fruit juice or yogurt to mask the taste and make it more palatable. Allocation to each group was performed with a number sequence based on a list randomly generated by a computer and which was only available for the pharmacist who prepared the sachets (the same pharmacy for the 4 centres), who did not have any information on the course of the study. The sequence was stratified by centre and was designed in blocks of 4. At inclusion patients were identified with a code. The list that related the code to the type of supplement was kept concealed until the end of the study.

Study Protocol

Standard treatment for preventing the recurrence of HE was non-absorbable disaccharides (lactulose or lactitol) adjusted to achieve 2 bowel movements per day. Neomycin (0.5 g bid) was prescribed for patients who did not tolerate non-absorbable disaccharides. For patients who were on diuretics, the dose was kept low to avoid predisposition to HE. If infection or gastrointestinal bleeding occurred, patients received standard treatment according to guidelines. During follow-up, patients developing an episode of HE with inadequate intake capacity were managed with an enteral tube feeding since the third day of admission until oral intake was re-established. In these cases, dietary supplements were supplied via enteral tube. HE duration was defined as the time between onset of

symptoms and maximal improvement of the episode. It was considered a failure of compliance with the diet when a patient did not achieve ≥ 80% of standard diet or dietary supplements for ≥ 80% of days of the study. To assess compliance with the diet a food intake record was used at baseline and at each visit, and the patients returned the empty sachets. Those patients who referred compliance < 80% with diet and oral supplements between two consecutive visits were withdrawn from the study.

Endpoints

The hypothesis proposed that the supplement of BCAA will reduce the recurrence of HE from 50% to 25%. The expected recurrence was based on the observed recurrence of HE in this population (1) and own unpublished data. The 25% reduction was selected because is considered clinically relevant (20). Accordingly, the primary endpoint of the study was HE-free survival. The secondary endpoints were days exhibiting HE during follow-up and differences at the end of follow-up on: minimal HE, chronic persistent HE (cognitive deficits that caused >2 days/week a Barthel's autonomy index < 80%), chronic recurrent HE (≥ 2 episodes in < 6 month), survival, health-related quality of life (HRQOL), nutritional status and liver function.

Outcomes

The duration of the study was 56 weeks. Clinical and dietetic visits were scheduled at 8, 16, 24, 32, 40, 48 and 56 weeks. There was an additional dietetic visit to assess compliance with diet and supplements at week 4.

Analytic and anthropometric parameters, neuropsychological tests and HRQOL questionnaires were performed at 8, 24, 40 and 56 weeks.

Nutritional status was assessed by the dietician who determined the following parameters: height, weight, body mass index, tricipital skinfold thickness (TSF), mid-arm muscle circumference (MAMC) and muscular strength (handgrip).

Minimal HE was evaluated by a psychologist (M.F.) who performed the Trail Making Test part A, Symbol Digit Test (oral version) and Grooved Pegboard Test (dominant hand). The scores of each test were transformed into *T*-values adjusted by age, sex and years of education based on the Spanish general population. The global cognitive function corresponds to the average of neuropsychological tests.

HRQOL was measured with the Spanish version of the Medical Outcomes Study Form (SF-36), which provides two summary scores (PCS, physical component score, and MCS, mental component score) (21), and the Chronic Liver Disease Questionnaire (CLDQ), which provides one summary score (global CLDQ) (22).

Sample size and statistical analysis

Assuming a two-sided α error of 0.05, a β error of 0.20 and considering a 25% difference in the recurrence of episodic HE at 56 weeks between two groups, a sample of 116 patients was calculated (58 per group).

Quantitative variables were compared between two groups using the Student´s *t*-test for unpaired data or the non-parametric Mann-Withney *U* test. Categorical variables were compared using the Pearson's X^2 test or the Fisher's exact test. Changes in quantitative variables during treatment were assessed

using the Student´s *t*-test for paired data or the Wilcoxon´s test. HE-free survival was assessed with the Kaplan-Meier method and the log-rank Mantel-Cox test. Patients were censored when they dropped out from the study (because of liver transplant, death or any other reason).

The analysis of variables that required a second assessment included only those patients who reached at least week 8. The last available variable was chosen for analysis of follow-up in patients who did not reach week 56. A multivariate analysis using a Cox regression model was performed to assess factors related to HE recurrence. The model was constructed from those variables that were statically significant in the univariate analysis; the group of treatment (BCAA or MDX) was also included. Variables that did not reach statistical significance were dropped from the final model.

RESULTS

Clinical Course

One hundred thirty-four patients were assessed for eligibility; of them 116 were randomized (Figure 1). There were no differences between groups in baseline characteristics (Table 1), duration of follow-up (BCAA=32.2 ± 21.6 weeks, MDX=36.3 ± 20.9 weeks, P=0.309), reasons for being censored before week 56, and causes of death (liver failure: 12 of 17; gastrointestinal bleeding: 3; others: 2). The majority of losses (n=18) before week 8 (first follow-up visit) were due to liver transplantation (n=8) or death (n=6).

Outcomes

HE-free survival was not significantly different between both groups (Figure 2). There were also no significant differences in number of patients who developed HE (BCAA=24, MDX=32, P=0.137). There was a trend towards a lower number of days on HE during follow-up in patients of the BCAA group (2.8 ± 5.2 vs. 5.1 ± 7.5), but the difference did not reach significance (P=0.1). In addition, there were no differences in the number of patients who developed chronic persistent HE (BCAA=6, MDX=5, P=0.7) or chronic recurrent HE (BCAA=14, MDX=16, P=0.6).

Two neuropsychological tests (Symbol Digit Test and Trail Making Test A) and MAMC improved in patients in the BCAA group, but not in the MDX group (Table 2). There were no significant changes in HRQOL and in the evolution of parameters of liver function (Table 2). The number of patients who were admitted to the hospital (BCAA=32, MDX=32, P=1.00) and the total number of

days hospitalized (NP-BCAA=9.8 ± 19.6, LP-MDX=7.4 ± 10.9, P=0.41) did not differ between both groups.

Recurrence of HE

In univariate analysis (Table 3), significant factors related to recurrence of HE were age (P=0.035), baseline albumin (P=0.011), Δ-creatinine (P=0.016) and Δ-sodium (P=0.026). In multivariate analysis, independent factors related to recurrence of HE were baseline albumin (g/dL; HR 0.429; IC95%: 0.255-0.721; P=0.001) and Δ-sodium (mEq/L; HR 0.938; IC95%: 0.892-0.983; P=0.012). The final Cox-regression model was statistically significant (X^2=21.014, *df*=3, P<0.005). The model included Δ-creatinine because was close to significance level (mg/dL; HR 1.849; IC95%: 0.903-3.789; P=0.09) and has been shown to be relevant in previous studies (23, 24).

The global cognitive function (Figure 3) showed an improvement during follow-up in patients who did not experienced episodes of HE (n=50), while remained stable (assessed after the episodes of HE) in those who developed bouts of HE (n=44). There were no differences in the MELD score between both groups (HE=16.5 ± 4.2, no-HE=15.2 ± 3.7, P=0.086). In addition, there was a correlation in the whole group of patients included in the study between the Δ-global cognitive function (final-baseline) and the number of episodes of HE (*r*=-0.328, P=0.001) (Figure 4).

DISCUSSION

The current study investigates the long-term effects of supplementing the diet with BCAA in patients with cirrhosis who have recovered from an episode of HE. The main finding is that the recurrence of HE is not different among patients who receive BCAA or MDX. The results are supported by lack of difference in the duration of encephalopathy and in the number of patients who developed chronic persistent or chronic recurrent HE.

A significant finding is the improvement in the BCAA group in two of the three neuropsychological tests that were evaluated. These tests measure attention, which is the most relevant feature of minimal HE (25). This result is in accordance with prior studies that have found benefits of BCAA for minimal HE (13,26), an effect that has been attributed to an improvement in liver function (17). In comparison to the study by Marchesini et al (17), we did not find differences in the evolution of parameters of liver function between the two groups. The most plausible reason for difference is that our patients exhibited a more advanced stage of liver disease, as corresponds to patients included on the basis of a previous episode of HE, which was not an inclusion criteria in the Italian trial. In our study the improvement of minimal HE could be an effect of an increase in the muscle mass, as indicated by a higher MAMC in the BCAA group. It is plausible that the anabolic effects of BCAA may increase MAMC, reduce plasma ammonia (not measured in our study) and improve minimal HE (27,28). However, the improvement in minimal HE observed with BCAA was mild and was not associated with changes in HRQOL.

The lack of a major impact of BCAA may be explained by the severity of liver failure. Malnutrition has been associated independently with prognosis only in

patients with mild to moderate liver failure (Child-Pugh A/B), who have an average life expectancy over 3 years (29). Nevertheless, our findings do not invalidate a possible beneficial effect of BCAA on the recurrence of HE. The 13% difference in favour of the BCAA group would have been significant with the inclusion of a sample of 446 patients. Thus, a type II error due to limited sample is possible. We set a priori that a clinically relevant difference would be a decrease in the recurrence rate of 25%. However, the difference in the range of 10-15% that was in favour of the BCAA group may be judged clinically relevant and may justify investigating further the role of BCAA in the prevention of HE recurrence.

An interesting finding of the current study is the identification of a series of variables that increased the risk of HE: baseline albumin, an increase in creatinine and a decrease in sodium. The relation between hyponatremia and HE is well described in observational studies (30), including one prospective study with repeated assessment in a group of patients with advanced cirrhosis (23). The theoretical basis is that hyponatremia may enhance astrocyte swelling by decreasing the amount of myoinositol and other organic osmolytes available to respond to an acute ammonia challenge (31). Recurrence of HE has also been related to mild increments in plasma creatinine (23,24). The increase in creatinine is probably an indicator of progressive circulatory dysfunction, which is pathophysiologically related to hyponatremia and hypoalbuminemia (32), the other two independent factors identified in the multivariable analysis. New therapies aimed at the prevention of circulatory dysfunction, with the combination of albumin and vasoconstrictors (33) may reduce the recurrence of HE. The efficacy of these therapies should be investigated in patients who

receive preventive therapy with non-absorbable disaccharides (34), and/or rifaximin (35).

The importance of the identification of factors that are associated with recurrence and are amenable to treatment is of special relevance after the recognition that HE may lead to irreversible consequences that persist after the resolution of the acute episode (36). We found that those patients who experienced episodes of HE after randomization did not show an improvement in their neuropsychological tests. The lack of the well known “learning effect” of repeated testing represents the acquisition of a defect in learning that adds to other cognitive disturbances present in these patients. Similar observations were recently reported by Bajaj JS et al (37), supporting the concept that the episodes of HE cause a decline in cognitive function.

One limitation of the current study is that the design does not allow discriminating between the effects of the amount of the nitrogen intake and its quality. We did not include a non-BCAA nitrogen supplement because it would have complicated the design and increased the number of patients. In the previous study by Marchesini et al, BCAA supplements were superior to an equinitrogenous protein intake (lactoalbumin). On the other hand, the current study provides the long-term effect in a large cohort of patients that is representative of an important number of patients who are discharged from the hospital (38). The high compliance with the diet and the thorough assessment of nutritional status, HRQOL and neuropsychological parameters confer an additional value to our results. The tolerance to BCAA supplements was good in the majority of our patients, but may be different in clinical practice. Future

studies in patients who have experienced an episode of HE should compare diets with a normal content of nitrogen that differ in the amount of BCAA.

In conclusion, the results of our study suggest that BCAA supplementation, initiated after an episode of HE, does not have a major impact on the recurrence of HE. Nevertheless, our data are in accordance with a beneficial effect of BCAA on minimal HE and muscle mass, but question the relevance of this improvement. The main determinant of the recurrence of HE appears to be the progression of liver failure, which offers scarce possibilities for nutritional intervention. Avoiding the recurrence of HE is a major goal in the management of patients with cirrhosis that in addition to reduce hospitalization may prevent cognitive decline. The characteristics of patients who showed recurrence of HE suggest that therapies for hyponatremia and circulatory dysfunction may be useful for this purpose.

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CONFLICT OF INTEREST / STUDY SUPPORT

Guarantor of the article: Dr. Juan Córdoba.

Specific author contributions:

Iñigo Les: selection and treatment of patients, acquisition of data, analysis and interpretation of data, drafting of manuscript.

Eduardo Doval: statistical analysis, critical review of manuscript.

Rita García-Martínez: treatment of patients, analysis and interpretation of data, critical review of manuscript.

Mercè Planas, Guillermo Cárdenas, Pilar Gómez: nutritional management of patients, monitoring of data.

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Beatriz Mínguez, Mercedes Vergara, Germán Soriano, Carmen Vila: selection and treatment of patients, acquisition of data.

Rafael Esteban: organization of the study, critical review of manuscript.

Juan Cordoba: obtaining funding, study concept and design, selection and treatment of patients, analysis and interpretation of data, drafting of manuscript, supervision of the study.

Statement of interests

1. Authors' declaration of personal interests:

The authors have nothing to declare.

2. Declaration of funding interests:

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STUDY HIGHLIGHTS

1. WHAT IS CURRENT KNOWLEDGE

The administration of BCAA to patients with cirrhosis prevents the progression of hepatic failure.

In patients with chronic HE, BCAA improves cognitive performance and allows providing adequate nitrogen supply.

2. WHAT IS NEW HERE

BCAA supplementation in patients who have experienced an episode of HE improves minimal HE.

BCAA supplementation does not have a major impact on preventing the recurrence of HE.

Recurrence of HE relates to circulatory dysfunction and hyponatremia and causes neuropsychological sequels.

FIGURE LEGENDS

Figure 1. Diagram of flow of participants of the study. There were no significant differences between both groups in duration of follow-up, causes of censoring and causes of death. MELD, model for end-stage liver disease; BCAA, branched-chain amino acids; MDX, maltodextrin.

Figure 2. Hepatic encephalopathy-free survival between BCAA group and MDX group. The actuarial risk of remaining free of HE did not differ between both groups (BCAA = 47%, MDX = 34%, P = 0.274). BCAA, branched-chain amino acids; MDX, maltodextrin.

Figure 3. Global cognitive function (average of neuropsychological tests, T-values) at baseline and in the last available determination in patients who where reassessed after the recurrence of hepatic encephalopathy (n=44) in comparison with those who did not develop hepatic encephalopathy during follow-up (n=50).

* P < 0.05 between baseline and final assessment.

Figure 4. Relationship between number of episodes of hepatic encephalopathy and changes (final-baseline) in global cognitive function (*T*-values).

Table 1. Baseline characteristics of patients randomized to BCAA group or MDX group

Characteristic	BCAA (n = 58)	MDX (n = 58)
Age (years)	64.1 ± 10.4	62.5 ± 10.4
Gender (male/female)	45/13	43/15
Etiology (HCV/alcohol/HCV+alcohol/other)	24/17/11/6	18/25/9/6
Child-Pugh	8.3 ± 2.0	8.1 ± 1.7
MELD	16.1 ± 4.5	16.2 ± 3.9
Minimal HE	18	22
Albumin (g/dL)	2.9 ± 0.6	2.9 ± 0.5
Bilirubin (mg/dL)	2.5 ± 1.4	2.7 ± 1.7
Prothrombin (INR)	1.7 ± 0.5	1.8 ± 0.7
Sodium (mEq/L)	137.6 ± 3.3	137.3 ± 3.8
Creatinine (mg/dL)	1.0 ± 0.4	1.0 ± 0.4
Therapy		
Non absorbable disaccharides	55	50
Neomycin	16	15
Diuretics	30	35
Betablockers	24	26

BCAA, branched-chain amino acids; MDX, maltodextrin; HCV, hepatitis C virus; MELD, model for end-stage liver disease; HE, hepatic encephalopathy; INR, international normalized ratio.
There were no significant differences between groups. Data are expressed as mean ± standard deviation or number.

Table 2. Outcome of neuropsychological tests, anthropometric parameters and HRQOL scores in patients who reached at least 8 weeks of follow-up

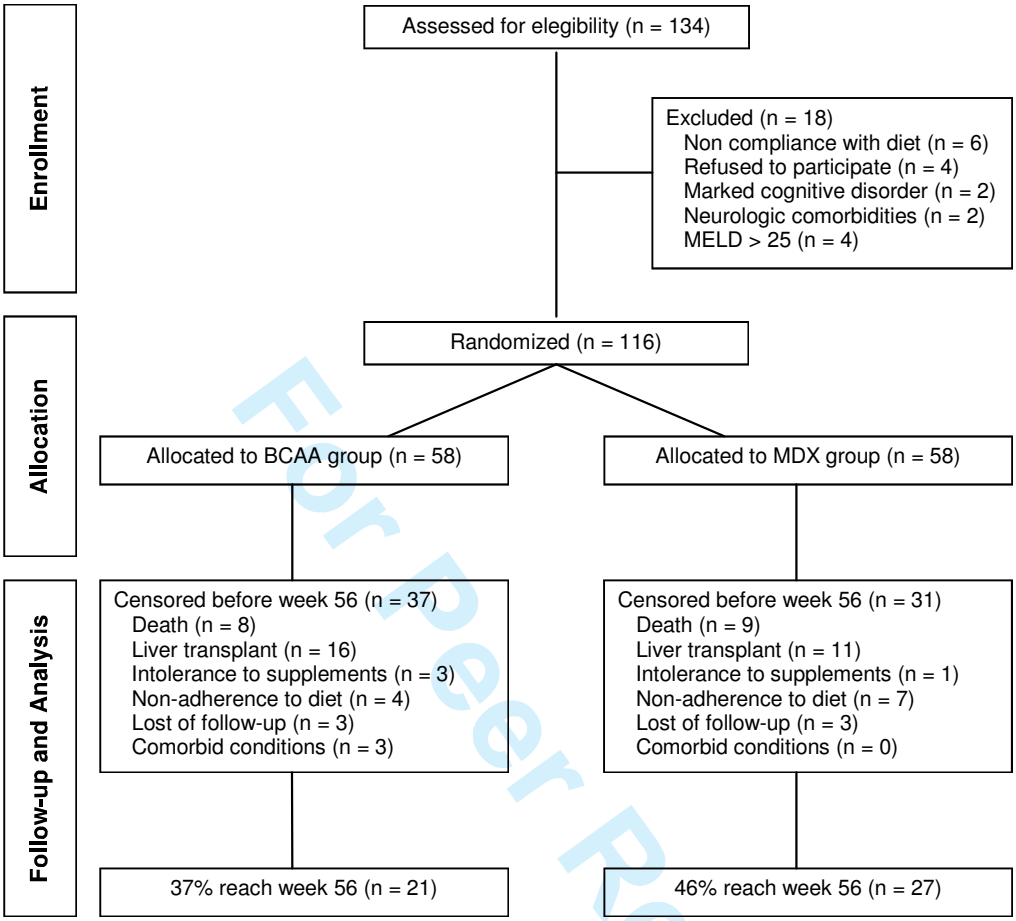
	BCAA (n = 46)		MDX (n = 52)	
Variable	**Baseline**	**Final**	**Baseline**	**Final**
Neuropsychology				
Symbol Digit test (oral)*	27.9 ± 12.3	30.5 ± 12.3†	25.9 ± 11.5	28.1 ± 13.6
Trail Making test A*	36.6 ± 8.2	39.1 ± 8.9†	36.5 ± 8.7	37.3 ± 9.4
Grooved Pegboard test*	39.0 ± 10.7	39.8 ± 11.2	35.7 ± 12.0	34.8 ± 11.0
Anthropometry				
MAMC (cm)	21.4 ± 3.0	22.2 ± 3.0†	22.1 ± 2.7	22.7 ± 3.3
Handgrip (kg)	20.6 ± 8.5	21.1 ± 8.4	22.1 ± 8.9	22.4 ± 8.7
HRQOL				
PCS of SF-36	34.8 ± 9.2	36.4 ± 10.5	37.3 ± 9.5	37.0 ± 10.2
MCS of SF-36	44.4 ± 13.8	45.7 ± 13.4	41.3 ± 14.9	42.5 ± 14.3
Global CLDQ	4.6 ± 1.0	4.7 ± 1.1	4.5 ± 1.2	4.4 ± 1.2
Liver parameters				
Child-Pugh score	8.3 ± 2.0	8.1 ± 2.0	8.0 ± 1.7	8.1 ± 2.1
MELD score	16.1 ± 4.5	15.6 ± 4.7	16.1 ± 3.9	16.5 ± 5.1

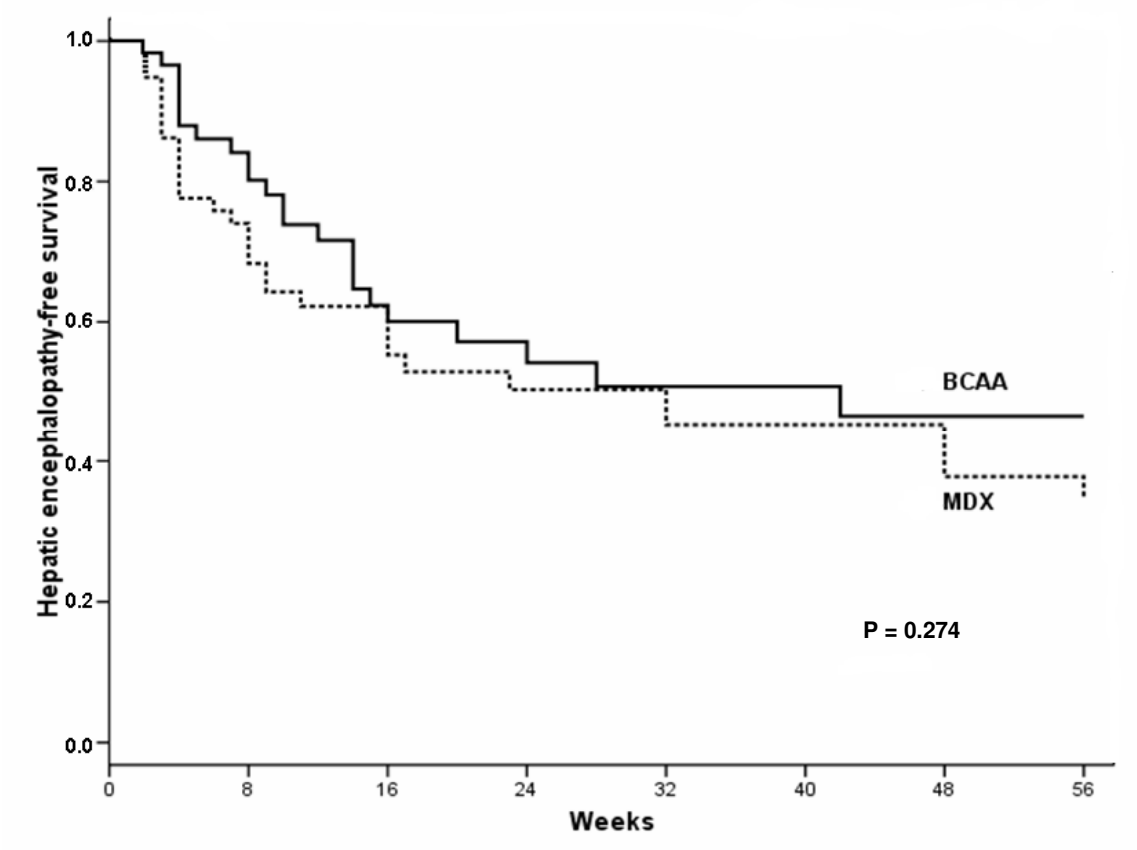
BCAA, branched-chain amino acids; MDX, maltodextrin; MAMC, mid-arm muscle circumference; HRQOL, health-related quality of life; PCS, physical component score; MCS, mental component score; CLDQ: chronic liver disease questionnaire; MELD, model for end-stage liver disease.
Data are expressed as mean ± standard deviation.
* *T*-scores.
† Final vs. baseline, P value < 0.05.

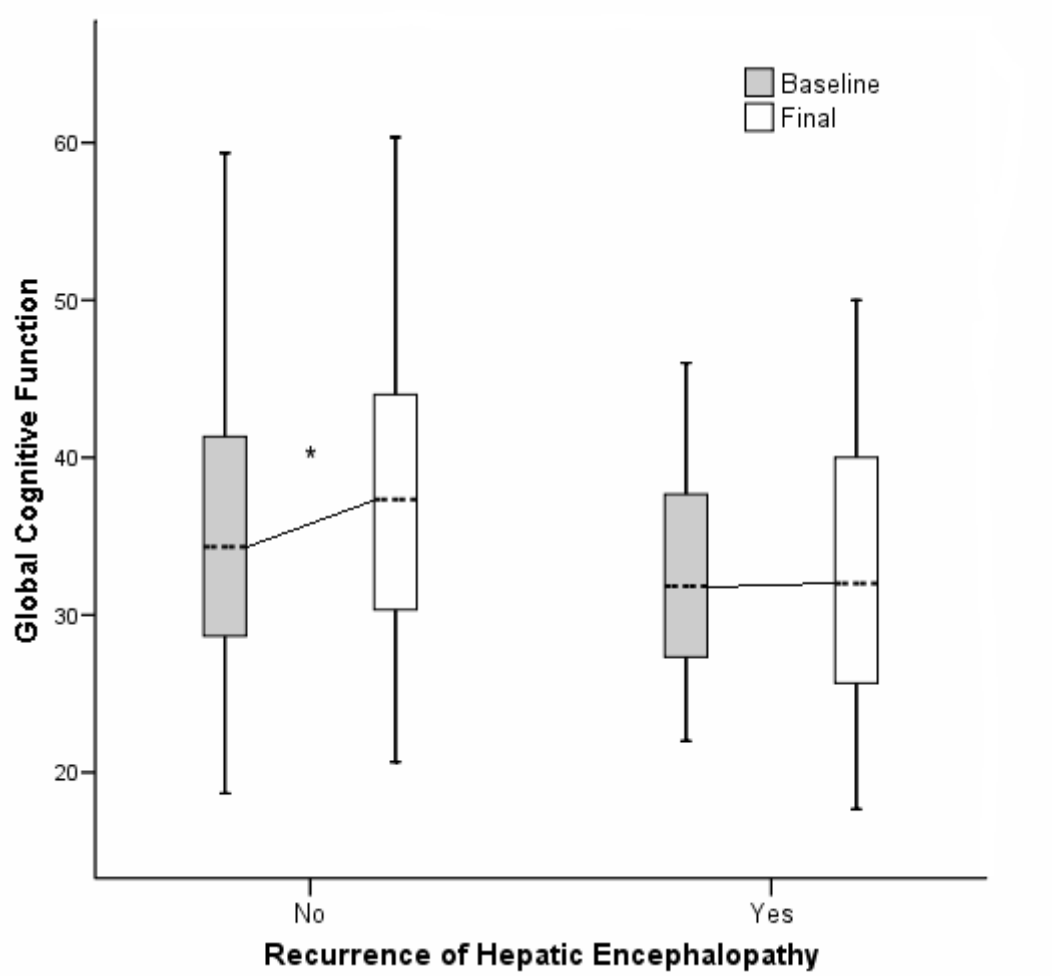
Table 3. Clinical parameters in relation to the recurrence of HE

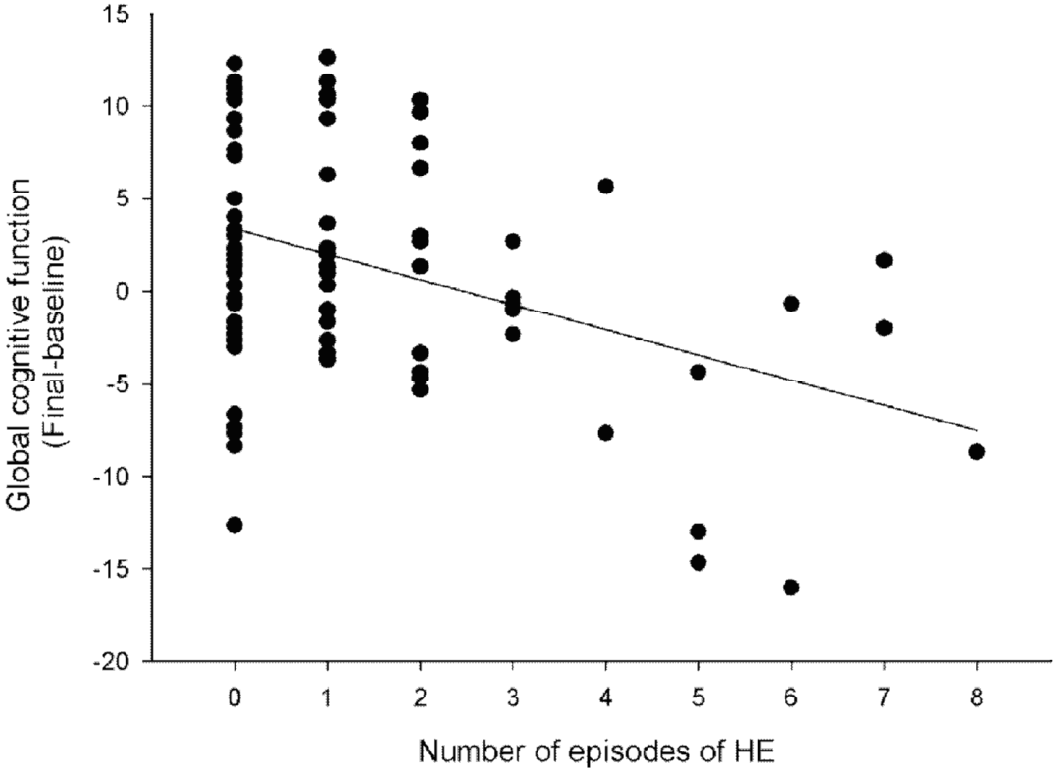
Variable	Recurrence (n = 56)	No recurrence (n = 60)	P value
Age (years)	65.41 ± 11.08	61.35 ± 9.37	0.035
β albumin (g/dL)	2.82 ± 0.53	3.07 ± 0.52	0.011
β bilirubin (mg/dL)	2.79 ± 1.70	2.53 ± 1.41	0.363
β prothrombin (INR)	1.76 ± 0.49	1.61 ± 0.45	0.106
β sodium (mEq/L)	137.81 ± 3.75	137.13 ± 3.41	0.309
β creatinine (mg/dL)	1.04 ± 0.41	1.05 ± 0.37	0.933
Δ albumin (g/dL)	0.09 ± 0.76	0.10 ± 0.68	0.959
Δ bilirubin (mg/dL)	0.20 ± 2.42	-0.34 ± 1.44	0.181
Δ prothrombin (INR)	0.07 ± 0.44	-0.05 ± 0.33	0.147
Δ sodium (mEq/L)	-2.00 ± 5.52	0.20 ± 3.91	0.026
Δ creatinine (mg/dL)	0.16 ± 0.33	0.00 ± 0.31	0.016

HE, hepatic encephalopathy; INR, international normalized ratio.
Data are expressed as mean ± standard deviation.
β = Baseline.
Δ = Increase (final - baseline).




Hepatic encephalopathy-free survival
1.0
0.8
0.6
0.4
0.2
0.0
0
8
16
24
32
40
48
56
Weeks
BCAA
MDX
P = 0.274


Baseline
Final
Global Cognitive Function
60
50
40
30
20
*
No
Yes
Recurrence of Hepatic Encephalopathy


Global cognitive function
(Final-baseline)
15
10
5
0
-5
-10
-15
-20
0
1
2
3
4
5
6
7
8
Number of episodes of HE