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BRIEF ARTICLE

Effect of branched-chain amino acids in patients receiving intervention for hepatocellular carcinoma

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Abstract

AIM: To investigate the usefulness of branched-chain amino acids (BCAA) before transarterial chemoembolization (TACE) or radiofrequency ablation (RFA).

METHODS: We investigated the usefulness of pre-intervention with BCAAs by comparing patients treated with BCAAs at 12.45 g/d orally for at least 2 wk before TACE or RFA and those not receiving such pretreatment. A total of 270 patients with hepatocellular carcinoma complicated by cirrhosis were included in the study. Mean changes from baseline (Δ) in serum albumin (Alb), C-reactive protein (CRP), and transaminase levels, as well as peak body temperature were also determined and compared at days 2, 5, and 10 after the start of TACE or RFA.

RESULTS: In patients who underwent TACE or RFA, BCAA pre-intervention significantly suppressed the development of post- intervention hypoalbuminemia and reduced inflammatory reactions during the subsequent clinical course. After TACE, the ΔAlb peaked on day 2, remained constantly lower in BCAA-treated patients, compared to the control group, and was -0.13 ± 0.42 g/dL in BCAA-treated patients and -0.33 ± 0.51 g/dL in untreated patients on day 10. The ΔCRP was also significantly lower in BCAA-treated patients on days 2, 5 and 10 after TACE. Like the trends noted after TACE, a similar tendency was noted as to the ΔAlb and ΔCRP after RFA. The changes in serum Alb level were inversely correlated with CRP changes; therefore, a possible involvement of the anti-inflammatory effect of BCAAs was inferred as a factor contributory to the suppression of decrease in serum Alb level.

CONCLUSION: Pre-intervention with BCAAs may hasten the recovery of serum Alb level and mitigate postoperative complications in patients undergoing TACE or RFA.

Key words: Branched-chain amino acids; Cirrhosis; Hepatocellular carcinoma; Transarterial chemoembolization; Radiofrequency ablation; Hypoalbuminemia

Core tip: This study investigated whether the short-term effect of branched-chain amino acid (BCAA) for transarterial chemoembolization (TACE) or radiofrequency ablation (RFA), focusing on BCAA treatment prior to therapeutic intervention, suppresses the decrease in serum albumin (Alb) level associated with TACE or RFA and reduces postoperative complications. We thought

that C-reactive protein (CRP) elevation was suppressed in BCAA-treated patients, that the severity of fever was milder as a result of BCAA treatment, and that the serum Alb level decreased to a lesser extent in patients with milder changes in CRP level.

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INTRODUCTION

Decrease in plasma albumin (Alb) level occurs early after therapeutic intervention such as transarterial chemoembolization (TACE) and radiofrequency ablation (RFA) for treatment of hepatocellular carcinoma (HCC), and the underlying mechanism of this condition includes the extravasation of Alb into the embolized or ablated hepatic region and the involvement of inflammatory cytokine[1]. HCC arises in association with cirrhosis in most patients, readily produces hypoalbuminemia, edema, ascites, and impairs the patient's quality of life, with a poor vital prognosis[2,3]. Measures to cope with hypoalbuminemia are needed in that therapeutic intervention options as well as the prognosis in HCC patients are dependent on this condition[4-7].

When administered to cirrhosis patients presenting with hypoalbuminemia, the branched-chain amino acids (BCAA) efficiently increase the Fisher ratio and thus improve hypoalbuminemia[8-13]. Improved event-free survival rate has been reported in patients with liver cirrhosis maintained on long-term continuous BCAA treatment[14,15], and the use of such treatment is recommended in guidelines in various countries[16]. In recent years, a liver-protective effect, *e.g.*, lessening of oxidative stress, of BCAAs has been attracting attention[17-19] and BCAA treatment has been reported to maintain skeletal muscles; these multifunctional pharmacological effects of this preparation have become the focus of increased interest[4].

Hypoalbuminemia is noted often early after TACE or RFA in patients with HCC complicated by cirrhosis[1]. This retrospective study was conducted to determine whether pre-intervention with BCAAs is effective in suppressing such hypoalbuminemia early after the intervention, as well as factors involved in such effect.

MATERIALS AND METHODS

A total of 270 patients with HCC complicated by cirrhosis who were admitted to Yokkaichi Digestive Disease Center and treated there between April 2004 and April 2012 were included in the study. TACE was performed in 162 patients (of them, 76 and 86 patients were treated with BCAAs and untreated before TACE, respectively) and RFA in 108 patients (of them, 40 and 68 patients were treated with BCAAs and untreated before RFA, respectively). Cirrhosis and HCC were diagnosed based on the findings in various imaging studies and hematological/blood chemical test results, and, where deemed necessary, liver biopsy and/or tumor biopsy findings were also used. Anticancer agents, cisplatin and epirubicin hydrochloride, were used in patients who underwent TACE. In the BCAA-treated group, patients received LIVACT® Granules (Ajinomoto Pharma Co., Ltd., Tokyo) at 12.45 g/d orally (in 3 divided doses daily, after each meal) for at least 2 wk before TACE or RFA, and the oral dosage of the drug remained unchanged throughout the study period. Patients who had not received such treatment constituted the non-BCAA-treated group (control group). Patients who received transfusion of Alb preparation, blood transfusion, and/or newly instituted BCAA treatment and patients who underwent TACE in combination with RFA during the course of study treatment were excluded from the study.

Patients were compared with respect to the following clinical parameters: pre-treatment (baseline) Child-Pugh score [serum Alb level, prothrombin time (PT) expressed as a percentage, total bilirubin (T-Bil), and severity of ascites/encephalopathy], clinical stage of HCC, maximum tumor diameter, C-reactive protein (CRP) level, and tumor markers. Mean changes from baseline (Δ) in serum Alb, CRP, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels, as well as peak body temperature were also determined and compared at days 2, 5, and 10 after the start of treatment.

Statistical analysis

Data obtained were expressed as the mean ± SD, and comparisons between the patient groups were performed using χ^2 test and *t* test. Changes in laboratory test parameters and body temperature from baseline (Δ) were analyzed using *t* test. Pearson's product-moment correlation coefficient was used for testing the correlation between the two groups.

RESULTS

Patient demographic characteristics of the two groups prior to TACE or RFA

Table 1 summarizes the demographic characteristics of patients who underwent TACE in this study. Patients in whom cirrhosis was etiologically not attributable to hepatitis virus were more frequent in the control group. There was a greater percentage of patients with advanced (stage-IVa) HCC in the BCAA-treated group although no significant difference was noted between the two groups in respect of maximum tumor diameter. BCAA-treated patients had a lower hepatic functional reserve, as indicated by a serum Alb level of 3.3 ± 0.4 g/dL, than non-BCAA-treated patients with a serum Alb level of 3.8 ± 0.5

Table 1 Characteristics of study groups underwent transarterial chemoembolization and radiofrequency ablation

Characteristics	TACE			RFA		
	Control group *n* = 86	BCAA group *n* = 76	*P* value	Control group *n* = 68	BCAA group *n* = 40	*P* value
Male/female	57/29	46/30	0.746	47/21	13/27	< 0.001
Age (yr)	72.2 ± 8.6	71.7 ± 7.2	0.055	71.9 ± 6.5	73.0 ± 6.0	0.386
Cause of hepatic cirrhosis (B/C/non B non C)	13/49/24	9/64/3	0.025	7/47/14	0/34/6	0.068
Child-Pugh (A/B/C)	11/1/1974	35/36/5	< 0.001	59/9/0	23/16/1	< 0.001
Child-Pugh score	5.6 ± 0.9	6.8 ± 1.4	< 0.001	5.7 ± 0.9	6.6 ± 1.1	0.001
HCC clinical stage (Ⅰ/Ⅱ/Ⅲ/Ⅳa/Ⅳb)	21/49/11/5/0	13/14/21/27/1	< 0.001	21/40/6/0/1	16/16/7/1/0	0.276
Alb (g/dL)	3.8 ± 0.5	3.3 ± 0.4	< 0.001	3.6 ± 0.4	3.2 ± 0.4	< 0.001
CRP (mg/dL)	1.0 ± 0.3	0.3 ± 0.5	< 0.001	1.0 ± 0.3	0.3 ± 0.5	0.010
Body temperature (℃)	36.2 ± 0.4	36.4 ± 0.5	0.006	36.3 ± 0.5	36.4 ± 0.4	0.006
PT	95% ± 10%	86% ± 15%	< 0.001	94% ± 10%	87% ± 14%	0.008
T-Bil (mg/dL)	0.9 ± 0.5	1.3 ± 1.1	0.007	0.8 ± 0.3	1.0 ± 0.5	0.014
AFP (ng/mL)	392 ± 70	1657 ± 434	0.009	392 ± 70	1657 ± 434	0.009
PIVKA-Ⅱ (mAU/mL)	334 ± 975	385 ± 1180	0.819	334 ± 975	385 ± 1180	0.819
Max tumor size (mm)	29 ± 26	29 ± 32	0.937	21 ± 8	20 ± 8	0.364

Data were assessed using student's *t* test. HCC: Hepatocellular carcinoma; Alb: Albumin; CRP: C-reactive protein; PT: Prothrombin time; T-Bil: Total bilirubin; AFP: α-fetoprotein; PIVKA-Ⅱ: Prothrombin induced by vitamin K absence-Ⅱ; TACE: Transarterial chemoembolization; RFA: Radiofrequency ablation; BCAA: Branched-chain amino acids.

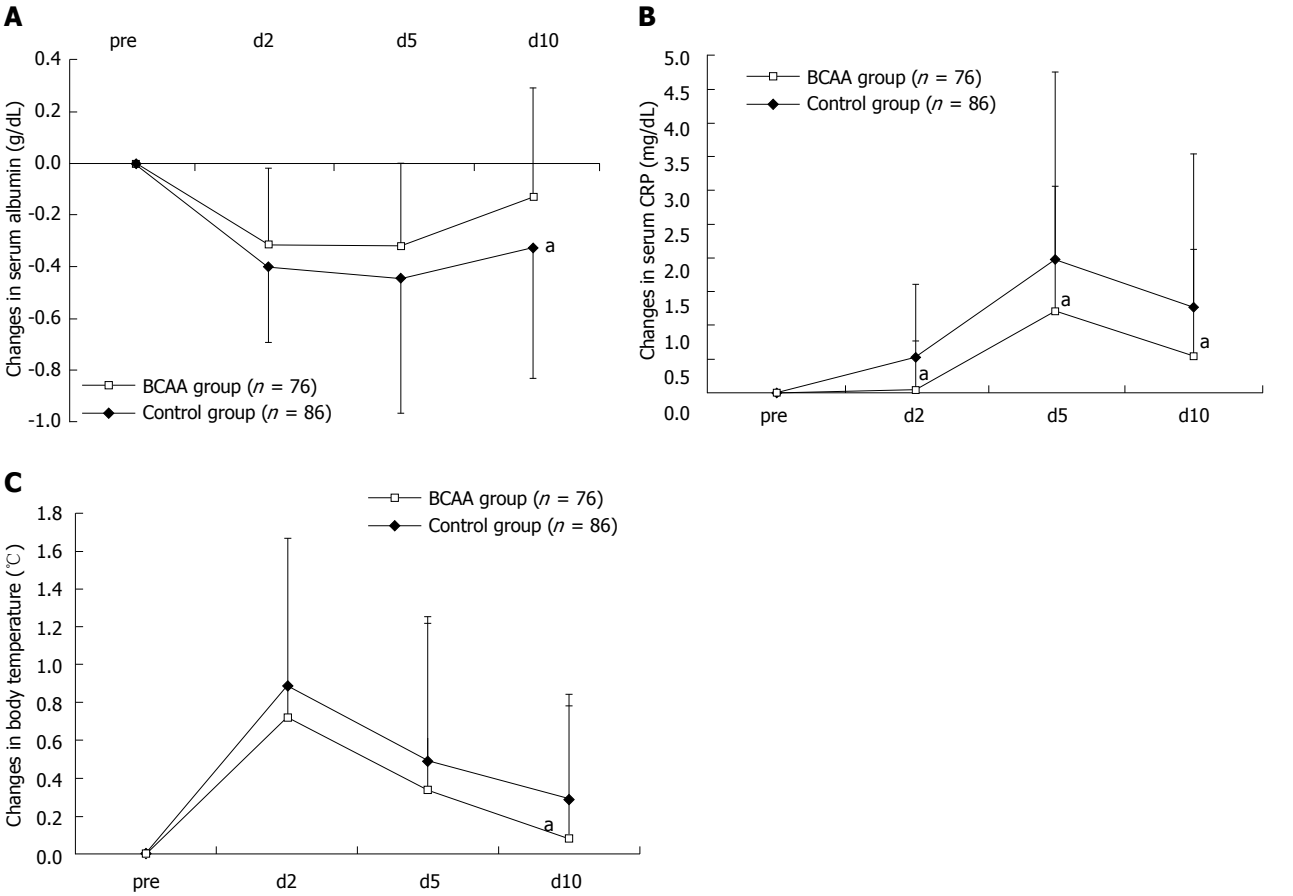

Figure 1 Changes in serum albumin (A), C-reactive protein (B) and body temperature (C) levels in comparison to the baseline level after transarterial chemoembolization. Data were assessed using student's *t* test (mean ± SD). $^{a}P < 0.05$ *vs* control group. CRP: C-reactive protein; BCAA: Branched-chain amino acids.

g/dL. PT% and T-Bil were also poorer in BCAA-treated patients; hence the significantly higher Child-Pugh score for these patients. The doses of cisplatin and epirubicin hydrochloride used in combination with TACE did not significantly differ between BCAA-treated and non-BCAA-treated patients. The demographic characteristics

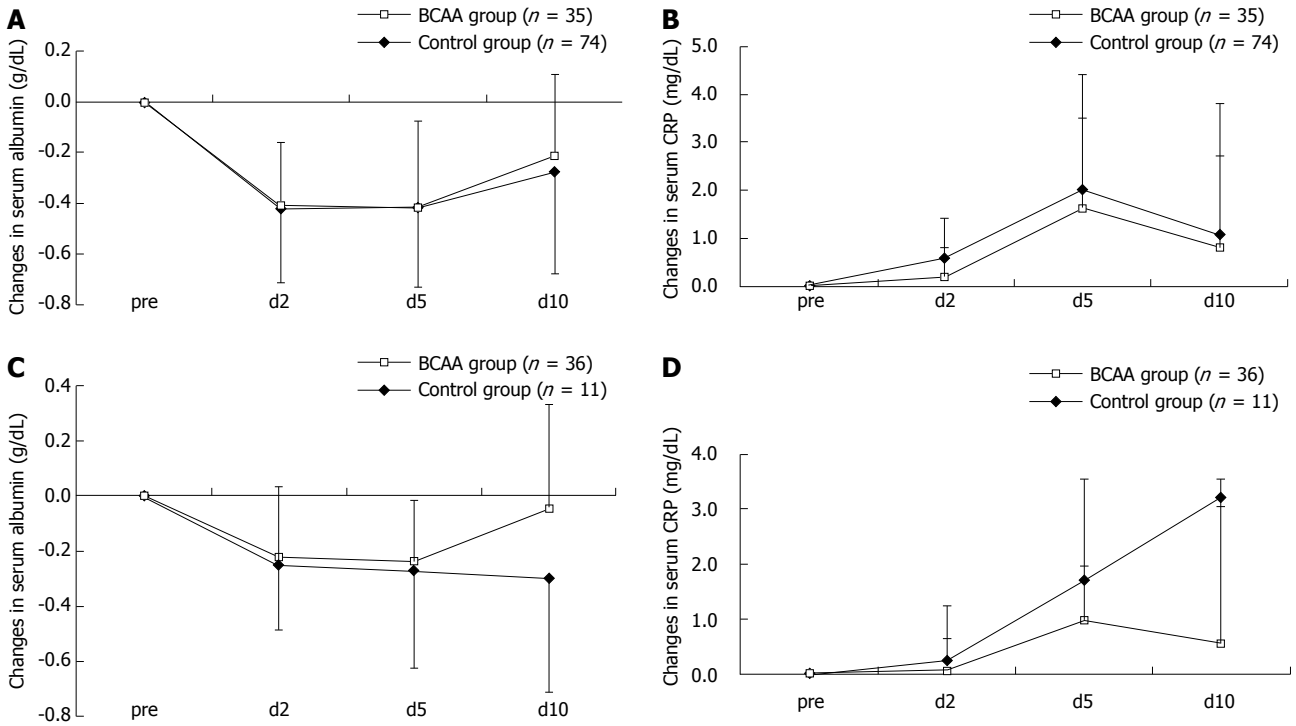

Figure 2 Comparison in Child A and B patients with serum albumin and C-reactive protein levels after transarterial chemoembolization. The analysis revealed a tendency for Child A patients to show a faster recovery in serum albumin level (A) and suppression of C-reactive protein (CRP) elevation (B). The analysis revealed a tendency for Child B patients to show a faster recovery in serum albumin level (C) and suppression of CRP elevation (D). Data were assessed using student's *t* test (mean ± SD). BCAA: Branched-chain amino acids.

of patients receiving RFA in this study are shown in Table 1. Depression of hepatic functional reserve, such as a significantly higher Child-Pugh score, was noted for the BCAA-treated group, as was the case with patients who underwent TACE. There was no significant difference between the BCAA-treated and non-BCAA-treated groups with respect to the cause of cirrhosis, clinical stage of HCC, or maximum tumor diameter.

Laboratory values and body temperature over time after TACE

After TACE, the ΔAlb peaked on day 2, remained constantly lower in BCAA-treated patients, compared to the control group, and was -0.13 ± 0.42 g/dL in BCAA-treated patients and -0.33 ± 0.51 g/dL in untreated patients on day 10, thus returning almost to the baseline level in the BCAA-treated group (Figure 1A). The ΔCRP was also significantly lower in BCAA-treated patients on days 2, 5 and 10 after TACE, and peaked on day 5 in both treated and untreated patients (Figure 1B). The maximum body temperature was significantly lower on day 10 post-TACE in the BCAA-treated group (Figure 1C). No significant difference was noted as to ΔAST or ΔALT between BCAA-treated and untreated patients.

As there was a significant difference in the hepatic functional reserve of BCAA-treated and untreated patients before TACE, we carried out an additional analysis with stratification by Child-Pugh A and B. The analysis revealed a tendency for Child A patients to show a faster recovery in serum Alb level and suppression of CRP elevation (Figure 2A and B). Child B patients exhibited the same trends (Figure 2C and D), indicating that responses to BCAA therapy were independent of pre-TACE hepatic functional reserve.

Laboratory values and body temperature over time after RFA

Like the trends noted after TACE, a similar tendency was noted as to the ΔAlb and ΔCRP after RFA; the elevation was suppressed in the BCAA-treated group (Figure 3). The ΔAlb and ΔCRP peaked on days 2 and 5 after RFA, respectively, in these groups, as with the case with these parameters after TACE. As seen in the case of TACE, no significant difference was observed in respect of ΔAST or ΔALT between BCAA-treated and untreated patients.

The stratified analysis of data on patients having undergone RFA also revealed a tendency for the serum Alb level to be recovered earlier and the CRP elevation to be suppressed (the suppression was significant especially in Child B on day 2) in both Child A and Child B patients, again indicating that pre-RFA hepatic functional reserve was unlikely to be involved in the patient response to BCAA therapy (Figure 4).

Correlation between ΔAlb and ΔCRP

The correlation between ΔAlb on day 2 post-TACE and ΔCRP on day 10 post-TACE tended to indicate that the greater the serum CRP elevation, the more decreased was the serum Alb level (Figure 5A). Furthermore, there was a significant negative correlation between ΔAlb on day 2

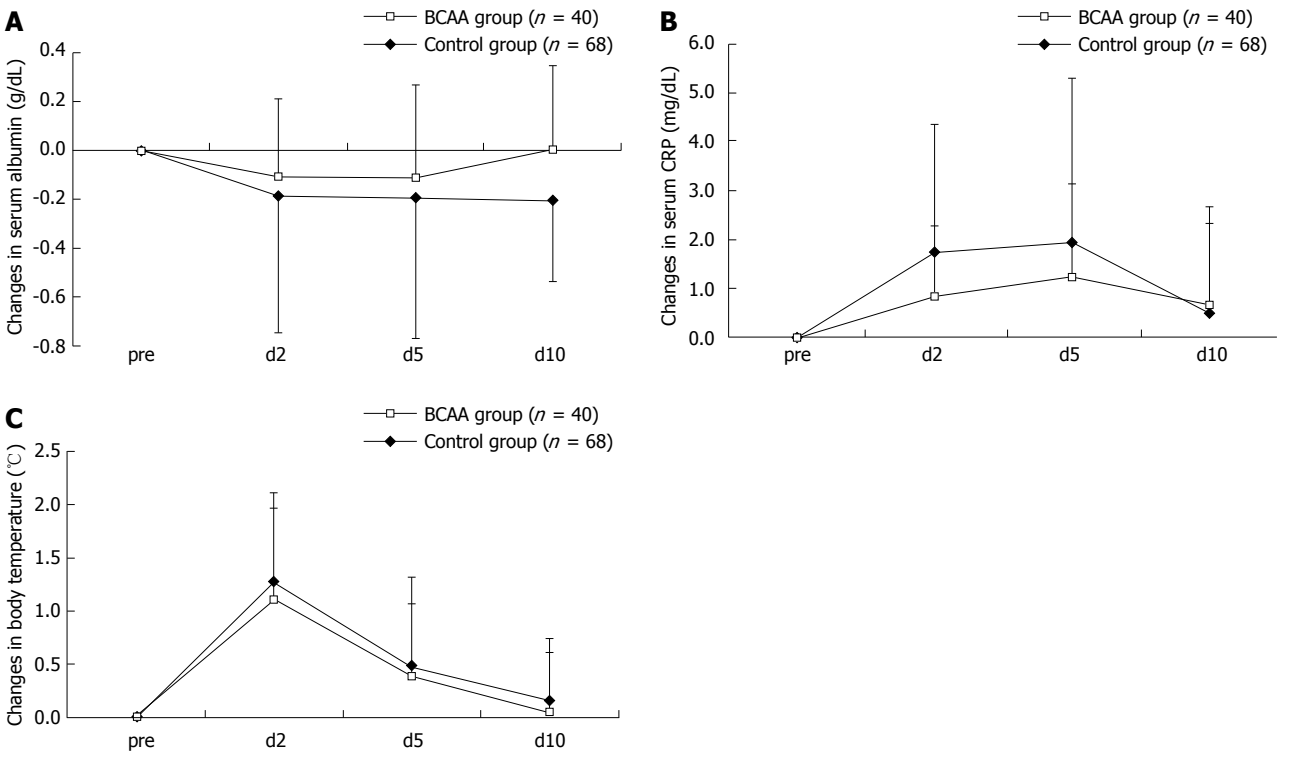

Figure 3 Changes in serum albumin (A), C-reactive protein (B) and body temperature (C) levels in comparison to the baseline level after radiofrequency ablation. Data were assessed using student's *t* test (mean ± SD). $^{a}P < 0.05$ *vs* control group. CRP: C-reactive protein; BCAA: Branched-chain amino acids.

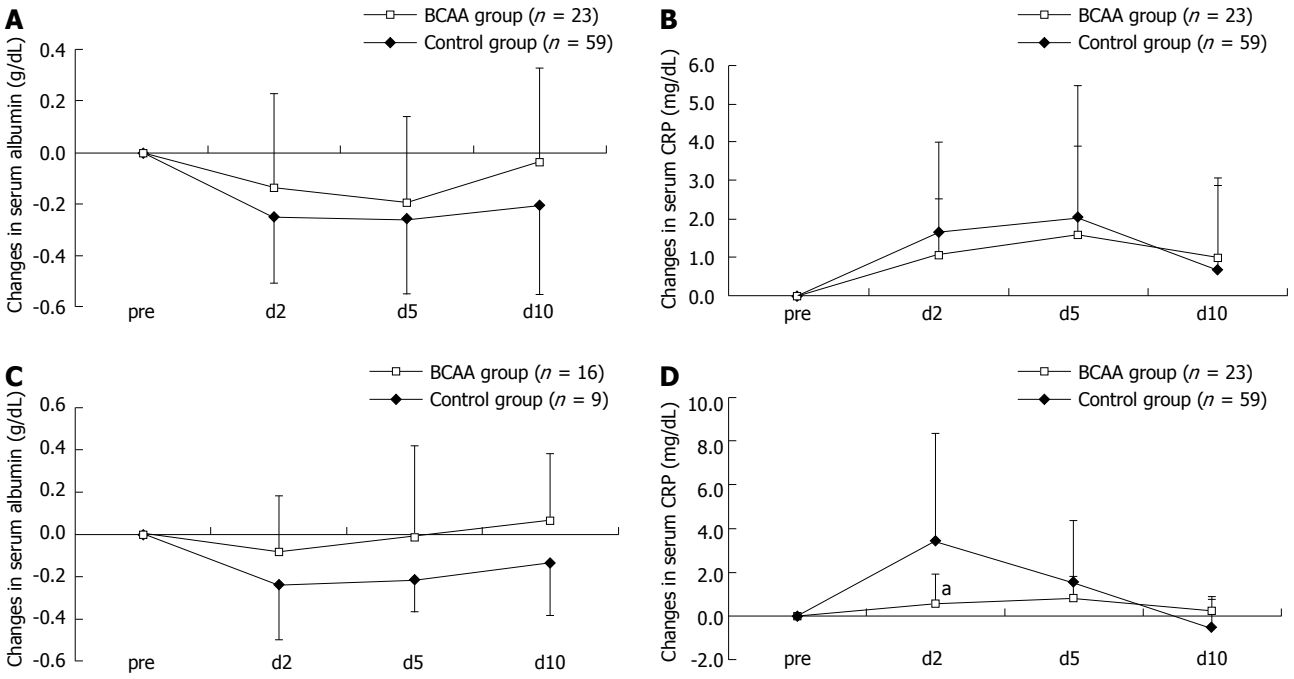

Figure 4 Comparison in Child A and B patients with serum albumin and C-reactive protein levels after radiofrequency ablation. A: A faster recovery of serum albumin level was noted in Child A; B: No difference of C-reactive protein (CRP) was noted in changes in Child A; C: A faster recovery of serum albumin level was noted in Child B; D: A significant difference of CRP was noted in changes in Child B. Data were assessed using student's *t* test (mean ± SD). $^{a}P < 0.05$ *vs* control group. BCAA: Branched-chain amino acids.

post-RFA and ΔCRP on day 10 post-RFA (Figure 5B). Analyses for correlation at time points of days 2, 5 and 10 revealed no significant correlation.

DISCUSSION

TACE and RFA are established treatment modalities for

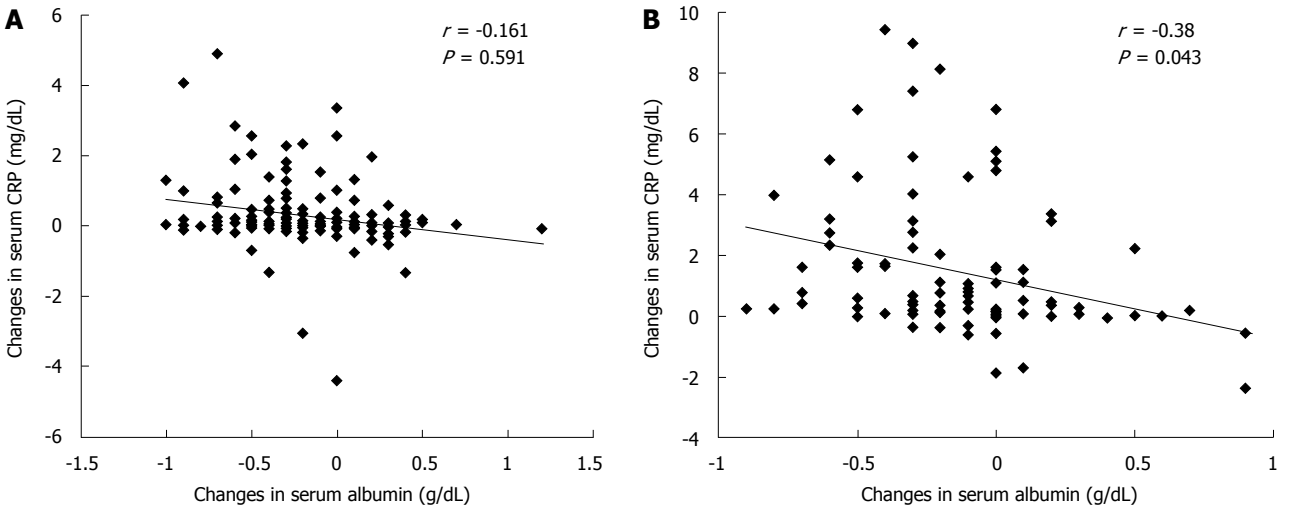

Figure 5 Relationship between Δalbumin (day 2) and ΔC-reactive protein (day 10). A: Transarterial chemoembolization; B: Radiofrequency ablation correlation between each variable was tested using Pearson's correlation coefficient.

hepatocellular carcinoma[20]. However, depression of hepatic functional reserve including hypoalbuminemia may develop after these therapeutic interventions[1]. It was reported that treatment with the BCAAs efficiently increases in Fisher ratio and improves hypoalbuminemia in cirrhosis patients presenting with hypoalbuminemia, and such treatment has become extensively used in daily clinical practice[4,5,14,15]. This effect is thought to result from enhanced mRNA translation for Alb with a consequent promotion of protein synthesis *via* activation of the mammalian target of rapamycin (mTOR) of hepatocytes that occurs in response to the BCAA supplement[21,22].

The effect of BCAA treatment on post-TACE hypoalbuminemia has already been investigated; Takeshita *et al*[23] reported that administration of BCAAs at 22:00 after every evening meal inhibited the development of hypoalbuminemia at 2 wk after TACE. Recently, Nishikawa *et al*[24] also reported that BCAA treatment was useful for long-term maintenance of nutrition after TACE in that the development of hypoalbuminemia was found to be suppressed at 1, 3, and 6 mo post-TACE. However, in the former study, nevertheless, patients had newly started BCAA treatment at the time TACE was performed, and the latter report does not refer to the changes during the early stage after TACE; the two reports differ from the present article in these respects.

On the other hand, based on their findings demonstrating a significant correlation between CRP elevation and decrease in serum Alb level, Koda *et al*[1] reported that the underlying mechanism of hypoalbuminemia developed following RFA was as follows: inflammatory cytokines liberated due to inflammation at the sites of cauterization act upon liver cells, thereby inducing production of acute inflammatory reactive proteins such as CRP and inhibiting Alb synthesis. They concluded that BCAA treatment was not effective in reversing a short-term decrease in serum Alb level early after RFA because there was no significant difference in serum Alb level decrease at 1 wk post-RFA between BCAA-pretreated and untreated patients[1].

The results of our review of a number of TACE- or RFA-treated patients demonstrated that the decline in serum Alb level was suppressed over 10 d post-treatment in BCAA-treated patients. BCAA pre-treatment might be effective in suppressing an early decline in serum Alb level after the therapeutic intervention. We inferred that the inflammation-inhibitory effect of BCAA treatment might be involved in the suppression of the decrease in serum Alb level[4,17-19] on the grounds that CRP elevation was suppressed in BCAA-treated patients, that the severity of fever was milder as a result of BCAA treatment, and that the decrease in serum Alb level was also to a lesser extent in patients with milder changes in CRP level. The following mechanism seemed likely to be operating: serum Alb level falls into a trough due to extravasation mainly into the embolized or ablated hepatic region as early as 2 d after TACE or RFA, and in patients receiving BCAA pre-treatment, its anti-inflammatory effect and sustained stimulation of mTOR from continued BCAA treatment lead to serum Alb level restoration nearly to the baseline level by day 10 post-intervention. While a direct hepatocyte damage-mitigating effect of BCAA treatment was demonstrated in an animal study[18,25,26], there was no significant difference in ΔAST or ΔALT between the BCAA-treated and untreated patients in this study; therefore, BCAA treatment is thought to be virtually devoid of hepatocyte damage-mitigating effect in the clinical setting.

The present results suggest that BCAA treatment prior to therapeutic intervention suppresses the decrease in serum Alb level associated with TACE or RFA and may reduce postoperative complications although confirmation of such effect observed in this study through prospective investigation and clarification of the underlying mechanism are needed.

COMMENTS

Background

Decrease in plasma albumin (Alb) level occurs early after therapeutic intervention such as transarterial chemoembolization (TACE) or radiofrequency ablation (RFA) for treatment of hepatocellular carcinoma (HCC). Measures to cope with hypoalbuminemia are needed in that therapeutic intervention options as well as the prognosis in HCC patients are dependent on this condition.

Research frontiers

When administered to patients with cirrhosis, branched-chain amino acids (BCAA) not only raises serum Alb level but also exerts a liver-protective effect such as lessening of oxidative stress. Authors investigated the usefulness of pre-intervention with BCAAs by comparing patients treated with BCAAs for at least 2 wk before TACE or RFA and those not receiving such pretreatment.

Innovations and breakthroughs

The inflammation-inhibitory effect of BCAA treatment might be involved in the suppression of decrease in serum Alb level on the grounds that C-reactive protein (CRP) elevation was suppressed in BCAA-treated patients, and that the decrease in serum Alb level was also to a lesser extent in patients with milder changes in CRP level.

Applications

Pre-intervention with BCAAs may hasten the recovery of serum Alb level and mitigate post-operative complications in patients undergoing TACE or RFA.

Terminology

In recent years, a liver-protective effect, *e.g.*, lessening of oxidative stress, of BCAAs has been attracting attention and BCAA treatment has been reported to maintain skeletal muscles; these multifunctional pharmacological effects of this preparation have become the focus of increased interest.

Peer review

The study found BCAA pre-intervention could significantly suppress the development of post-operative hypoalbuminemia and reduce inflammatory reactions during the subsequent clinical course in 162 patients, the changes in serum Alb level were inversely correlated with CRP changes. It is very important for patients with HCC to avoid hypoalbuminemia after the treatment of TACE or RFA.

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