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The Role of 8% Branched Amino Acids (BCAA) in Patients with Hepatic Encephalopathy

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ABSTRACT

Hepatic Encephalopathy (HE) is a neuropsychiatric disorder caused by liver dysfunction, commonly seen in cirrhosis or acute liver failure. **Objective:** To address the safety and efficacy of branched-chain amino acids (BCAA) solution in patients with HE. **Methods:** This retrospective study was performed at the Sheikh Khalifa Bin Zayed Al Nahyan Hospital, CMH Rawalakot, Azad Kashmir, Pakistan. Data from patients fulfilling the eligibility criteria during the study span from February 2022 to August 2024 were analyzed. The inclusion criteria were adults aged 18-70 years, diagnosed cases of cirrhosis of the liver, and admitted with HE. The BCCA group was given 8% BCCA solution administered through intravenous (IV) transfusion. Patients receiving any other treatments were categorized as conventional treatment. Psychometric hepatic encephalopathy score (PHES), serum ammonia levels, duration of hospitalization, treatment-related adverse events, and mortality were documented. **Results:** 467 patients were analyzed, the median age was 54.00 (48.00-63.00) years, and 280 (60.0%) were male. 315 (67.5%) received IV BCAA, while the remaining 152 (32.5%) received conventional therapy. Patients in the BCAA group showed a significant improvement in PHES scores, (-2.1 ± 1.9 vs.-4.6 ± 2.2, p=<0.001), reduction in serum ammonia levels (45.3 ± 8.1 vs. 56.2 ± 10.8 µmol/L, p<0.001), mean duration of hospitalization (8.9 ± 3.7 vs. 10.1 ± 4.5 days, p=0.002), and mortality (3.8% vs. 9.2%, p<0.001). In the BCAA group, 8 (2.2%) patients experienced mild gastrointestinal discomfort, and 4 (1.3%) patients reported transient dizziness. **Conclusions:** Intravenous 8% BCAA solution effectively enhances cognitive function, lowers serum ammonia, shortens hospitalization, and reduces mortality in hepatic encephalopathy patients.

INTRODUCTION

Hepatic Encephalopathy (HE) is a complex neuropsychiatric disorder that arises as a result of liver dysfunction, most frequently observed in patients with cirrhosis or acute liver failure. HE is characterized by the accumulation of toxic substances, primarily ammonia, in the bloodstream [1]. Normally, the liver detoxifies ammonia; however, in the presence of liver dysfunction, ammonia levels rise and accumulate in the brain, leading to cognitive impairments ranging from mild confusion to deep coma [2]. The pathophysiology of HE is explained by the direct toxicity of ammonia and alterations in neurotransmission, neuroinflammation, and oxidative stress [3]. HE is estimated to affect as many as 40% of cirrhotic patients with varying degrees of severity depending upon the extent of disease [4]. Data reports 30-40% of hospitalized cirrhotic patients developing overt HE, while the presence of HE is expected to worsen the overall progress of cirrhosis of the liver [5,6]. Standard treatments for HE typically focus on reducing ammonia levels in the bloodstream. The most common interventions include dietary protein restriction, the use of lactulose, and the administration of rifaximin [7]. While these therapies are

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widely used and can be effective. Recent research has suggested that branched-chain amino acids (BCAAs) may offer a novel approach to managing HE by modulating ammonia metabolism and neurotransmitter function [8]. BCAAs, which include leucine, isoleucine, and valine, are essential amino acids involved in protein synthesis and energy metabolism [9]. Emerging evidence suggests that BCAAs may also improve cognitive function in HE patients by serving as an alternative substrate for ammonia detoxification. BCAAs have been shown to influence neurotransmitter synthesis, particularly by modulating the balance between excitatory and inhibitory neurotransmitters in the brain [10]. Utilization of BCAAs in HE is gaining attention due to their potential role in reducing ammonia levels and restoring the neurochemical balance in the brain. BCAAs compete with aromatic amino acids for transport into the brain, thereby reducing the influx of ammonia and improving neurotransmitter balance [11]. Given the significant morbidity and mortality associated with HE, the need for alternative, more effective treatments is pressing. While global research on BCAAs in HE is abundant, local data in Pakistan is scarce. This gap in local evidence underscores the need for further investigation into the efficacy of BCAAs in HE.

This study aimed to address the safety and efficacy of BCAA solution in patients with HE. By assessing clinical outcomes such as cognitive function and ammonia levels, the findings of this study may help in determining whether BCAA can serve as a valuable option to current HE therapies.

METHODS

This retrospective study was performed at the Sheikh Khalifa Bin Zayed Al Nahyan Hospital, CMH Rawalakot, Azad Kashmir, Pakistan. Data of all patients fulfilling the eligibility criteria during the study span from February 2022 to August 2024 were analyzed. Exemption from Institutional Ethical Committee was obtained for conducting this research (PMC/RKT/15/2024). The inclusion criteria were adults aged 18-70 years, diagnosed cases of cirrhosis of the liver, and admitted with hepatic encephalopathy (HE) based on clinical features and confirmed by ammonia levels and neuropsychiatric testing. Data of patients with end-stage liver disease requiring liver transplantation, pregnancy, or lactation were excluded. Patients with other neurological disorders, including stroke, dementia, or epilepsy, chronic renal failure, or heart failure, were also excluded. HE was defined based on clinical symptoms and elevated serum ammonia levels (greater than 50 µmol/L) by the attending consultant gastroenterologist at the time of diagnosis. Demographic characteristics like gender, age, and area of residence were noted from hospital records. Clinical information, like etiology of cirrhosis, Child-Pugh class, presence of comorbidities, and psychometric hepatic encephalopathy score, was also documented from the hospital record. Patients were either categorized as BCCA treated or conventional treatment based on the treatment they received. Patients who had received 8% BCCA solution administered through intravenous (IV) transfusion (Aminoleban by Otsuka Pakistan Ltd) were labeled as the BCCA-treated group. Patients receiving any other treatments like lactulose, rifaximin, or other supportive care like electrolyte management, diuretics, or nutritional support were categorized as conventional treatment. The BCAA solution was administered as 500 ml twice a day over 4 to 6 hours, for 5-7 days, with the dosage adjusted according to clinical response and ammonia levels [12]. If any adverse events were observed or if significant improvements in cognitive function and ammonia levels occurred, the dosage was reduced. Regular monitoring of ammonia levels, as well as renal and liver function, was made to ensure safety and guide appropriate dose adjustments. All patients received standard care for liver disease, including management of underlying cirrhosis, based on their clinical needs. The treatment was provided by the medical team under the supervision of attending physicians and a consultant gastroenterologist managing HE cases. The BCAA solution was administered by trained healthcare staff, including nurses, under the supervision of the treating physicians. The primary outcome included evaluation of cognitive function improvement through analysis of psychometric hepatic encephalopathy score (PHES). The PHES evaluation was conducted by a team of trained healthcare professionals, including a consultant neurologist, hepatologists, and a specialized medical staff, as part of the routine assessment for patients with HE. PHES involves various psychometric tasks, including timed reaction tests, digit-symbol substitution, and other cognitive assessments that have been validated for detecting HE. Secondary outcomes were recorded from the hospital records, in the form of serum ammonia levels (pre-treatment and after 1 week), duration of hospitalization, treatment-related adverse events, and mortality. Data analysis was performed using IBM-SPSS Statistics, version 26.0. Continuous variables were summarized using mean and standard deviation (SD) or median and interquartile range, and categorical variables were shown using frequencies and percentages. The characteristics and outcomes in patients were compared using an independent sample t-test (for normal distribution) or the Mann-Whitney U test (for skewed data), or the chi-square test. Kaplan-Meier curves were estimated to conduct survival analysis, applying the log-rank test. A $p<0.05$ was considered statistically significant.

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RESULTS

Data from 520 patients were initially screened for eligibility. After excluding 53 patients due to conditions such as end-stage liver disease (n=18), pregnancy (n=5), lactation (n=1), neurological disorders (n=8), chronic renal failure (n=11), and heart failure (n=10), 467 patients were considered for this study (Figure 1).

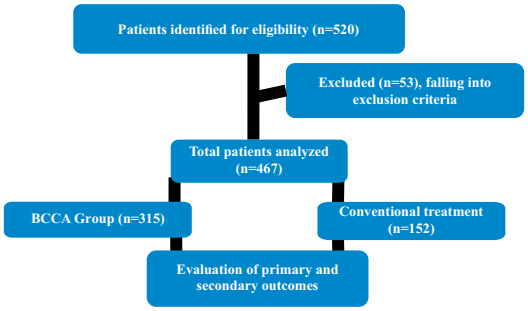

Figure 1: Study Flow Diagram

In 467 patients analyzed, the median age was 54.00 (48.00-63.00) years, and 280 (60.0%) were male. The residential status of 288 (61.7%) patients was rural. There were 228 (48.8%) who were having Child-Paugh Class-B. Hypertension was the common comorbidity, noted in 197 (42.2%) patients. Baseline serum ammonia level was 75.4 ± 21.7 umol/L. Baseline mean PHES was 6.4 ± 2.2. Of the total 467 patients, 315 (67.5%) received BCAA, while the remaining 152 (32.5%) received conventional therapy. Concerning treatment given, there was no significant differences regarding age (p=0.204), gender (p=0.819), residence (p=0.958), etiology of liver disease (p=0.389), Child-Paugh Class (p=0.939), diabetes mellitus (p=0.416), hypertension (p=0.533), renal dysfunction (p=0.401), serum ammonia level (p=0.401), and PHES (p=0.651), and the details are shown in Table 1.

Table 1: Characteristics of patients with hepatic encephalopathy (n=467)

Variables	Category	Total Range/ Frequency (%)	BCAA-Treated Group Range/ Frequency (%) (n=315)	Conventional Treatment (n=152)	p-Value
Age	Median (Interquartile Range) Years	54.00 (48.00-63.00)	56.00 (48.00-63.00)	54.00 (48.00-59.75)	0.380
Gender	Male	280 (60.0%)	190 (60.3%)	90 (59.2%)	0.819
	Female	187 (40.0%)	125 (39.7%)	62 (40.8%)	
Residence	Rural	288 (61.7%)	194 (61.6%)	94 (61.8%)	0.958
	Urban	179 (38.3%)	121 (38.4%)	58 (38.2%)	
Child-Paugh Class	A	176 (37.7%)	120 (38.1%)	56 (36.8%)	0.939
	B	228 (48.8%)	152 (48.2%)	76 (50.0%)	
	C	63 (13.5%)	43 (13.7%)	20 (13.2%)	
Comorbidities	Diabetes mellitus	148 (31.7%)	96 (30.5%)	52 (34.2%)	0.416
	Hypertension	197 (42.2%)	136 (43.2%)	61 (40.1%)	0.533
	Baseline renal dysfunction (serum creatinine > 1.5 mg/dl)	55 (11.8%)	39 (12.4%)	16 (10.5%)	0.560
Baseline serum ammonia (µmol/L)		75.4 ± 21.7	76.6 ± 21.3	74.8 ± 22.5	0.401
Psychometric Hepatic Encephalopathy Score		-6.4 ± 2.2	-6.4 ± 2.3	-6.5 ± 2.1	0.651

Patients in the BCAA group showed a significant improvement in PHES scores, with a mean change from -6.4 ± 2.2 at baseline to -2.1 ± 1.9 after treatment, in contrast to conventional treatment with a baseline of -6.4 ± 2.3 to -4.6 ± 2.2 (p <0.001). Patients in the BCAA group demonstrated a significant reduction in serum ammonia levels, with a mean decrease from 75.4 ± 21.7 umol/L at baseline to 45.3 ± 8.1 µmol/L after treatment, in comparison to baseline levels of 76.6 ± 21.3 µmol/L to 56.2 ± 10.8 µmol/L with conventional treatment (p<0.001). The mean duration of hospitalization was significantly shorter in the BCAA group (8.9 ± 3.7 vs. 10.1 ± 4.5 days, p=0.002). In the BCAA group, 8 (2.2%) patients experienced mild gastrointestinal discomfort, and 4 (1.3%) patients reported transient dizziness. Mortality was significantly less among patients who were given BCCA (3.8% vs. 9.2%, p<0.001). In Child-Pugh Class A, mortality was noted in 2 patients in the BCAA-treated group versus 3 in the conventional treatment group. In Child-Pugh Class B, 5 patients died in the BCCA patients, versus 4 in the conventional treatment group. In Child-Pugh class C, 5 patients died in the BCAA treatment group versus 7 in conventional treatment. There was no significant difference in mortality and various Child-pugh classifications (p=0.781). The comparison of primary and secondary outcome details between BCCA and conventional treatment is shown in Table 2.

Table 2: Comparison of primary and secondary outcomes in patients with hepatic encephalopathy (n=467)

Outcomes	BCAA-Treated Group (n=315)	Conventional Treatment (n=152)	p-Value
Psychometric Hepatic Encephalopathy Score	-2.1 ± 1.9	-4.6 ± 2.2	<0.001
Serum ammonia (umol/L)	45.3 ± 8.1	56.2 ± 10.8	<0.001
Duration of hospitalization	8.9 ± 3.7	10.1 ± 4.5	0.002

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Adverse Events	Gastrointestinal discomfort	8 (2.2%)	-	0.047
	Transient dizziness	4 (1.3%)	-	0.163
	Nausea	-	5 (3.3%)	0.001
Mortality		12 (3.8%)	14 (9.2%)	0.017

Survival analysis showed statistically significant differences between both study groups (p=0.035), and the details are depicted in Figure 2.

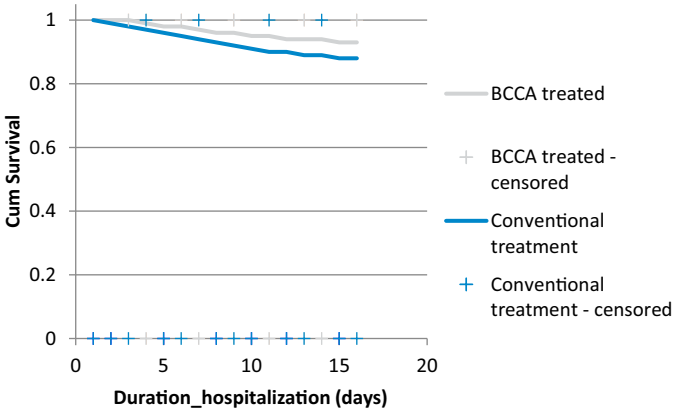

Figure 2: Kaplan-Meier survival analysis between study groups

DISCUSSION

The findings of this study indicate that BCAA supplementation is effective in improving cognitive function, reducing ammonia levels, and decreasing the length of hospitalization in patients with HE. These results provide compelling evidence for the therapeutic potential of BCAA supplementation in patients with HE. A Cochrane systematic review by Gluud *et al.*, which included 16 randomized clinical trials with 827 participants, found that BCAA supplementation significantly improved HE (RR 0.73, 95% CI 0.61 to 0.88) [13]. They also found no significant effect of BCAA on mortality, but reported improvements in HE symptoms. The present study reported significantly better survival among patients using BCAA, which contradicts the findings of Gludd *et al.,* [13]. Dam *et al.,* found beneficial effects of BCAA on HE and emphasized the ammonia-lowering effects of BCAAs, which is consistent with the present findings [14]. The reduction in ammonia levels in the BCAA group in this study (from 76.6 to 45.3 µmol/L) further supports the hypothesis that BCAAs may help lower ammonia levels through muscle metabolism, as suggested by Dam *et al.*, and Holeček [14, 15]. These findings are important because elevated ammonia is a key neurotoxic mediator in HE, and its reduction could be a mechanism through which BCAAs exert their cognitive benefits [16]. Marrone *et al.*, highlighted that the BCAA-induced balance of amino acids could be associated with improved HE symptoms [17]. Afridi *et al.*, in a local study, observed that BCAA supplementation was more effective than conventional therapy in improving clinical outcomes in patients with HE due to cirrhosis [12]. Afridi *et al.*, adopted a similar methodology with a randomized controlled trial design and showed significant clinical improvement in the BCAA group, which mirrors the current results in terms of PHES and ammonia levels [12]. While there is a wealth of studies supporting the benefits of BCAAs, particularly on cognitive outcomes and ammonia reduction, the differences in results across studies can often be attributed to factors such as the administration route (oral vs intravenous), the duration of supplementation, and variations in patient populations. The IV BCAA administration may provide more immediate therapeutic effects, as observed in this study, compared to oral supplementation, which may take longer to achieve clinical improvements [18]. The clinical implications of the present study are significant.HE is a common and debilitating complication of liver cirrhosis and other liver diseases, associated with significant morbidity, mortality, and healthcare costs [19, 20]. Current treatments, such as lactulose or rifaximin, are effective in reducing ammonia levels; their role in addressing the underlying neurochemical disturbances in the brain remains questionable [21].The introduction of BCAA supplementation could provide an additional avenue for improving cognitive function, reducing ammonia levels, and shortening hospitalization times in patients with HE. This study demonstrated a significant reduction in the length of hospitalization in the BCAA group, which is particularly important in a clinical setting where reducing hospital stays can help alleviate the burden on healthcare systems and reduce associated costs. The low incidence of adverse events (e.g., gastrointestinal discomfort, transient dizziness) in the BCAA group further underscores the safety of this therapy [22, 23]. Given that HE is a progressive condition and patients often experience repeated episodes, BCAA supplementation could also play a role in improving long-term outcomes, such as reducing the risk of recurrent HE episodes and improving overall quality of life. Several limitations of this research should be noted. The study design was retrospective, which limits the ability to draw definitive conclusions about causality. Although the results are compelling, further randomized controlled trials are needed to confirm the efficacy of BCAA supplementation in larger and more diverse patient populations. While this study observed significant improvements in cognitive function and serum ammonia levels, the long-term benefits of BCAA supplementation in patients with HE remain unclear.Longer-term studies

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would provide valuable insights into the sustainability of these improvements and the potential impact on liver disease progression and survival.Future studies should include a broader range of liver disease etiologies to determine whether BCAA supplementation is equally effective in these groups.

CONCLUSIONS

This study demonstrates that the intravenous administration of 8% BCAA solution is effective in improving cognitive function, lowering serum ammonia levels, reducing the duration of hospitalization, and decreasing mortality in patients with hepatic encephalopathy. These findings support the use of BCAA supplementation in the management of HE. BCAA supplementation could be considered an important addition to the therapeutic armamentarium for HE.

Authors Contribution

Conceptualization: AS
Methodology: RS, HM, MAQ, AS
Formal analysis: MAQ, RM, RS, HM
Writing review and editing: AS, MAQ, AM, RS, HM

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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