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Evaluation of the Efficacy of Branched Chain Amino Acids in the Management of Hepatic Encephalopathy Secondary to Liver Cirrhosis.

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Abstract

Background: Hepatic encephalopathy is a common neuropsychiatric complication of cirrhosis, associated with significant morbidity and mortality. Its management remains challenging despite available therapies. Branched chain amino acids (BCAAs) have been proposed as an adjunct treatment, but their clinical efficacy remains controversial. This study evaluated BCAAs in patients with cirrhosis-related hepatic encephalopathy.

Objective: To assess the efficacy of branched chain amino acids in improving consciousness levels in patients with hepatic encephalopathy secondary to liver cirrhosis, using the West-Haven classification for clinical grading.

Study design: A Descriptive Case Series.

Place and duration of study: Department of Gastroenterology Ward Ayub teaching hospital abbottabad from jan 2023 to jan 2024

Methods: This descriptive case series was conducted in the Department of Gastroenterology, Ayub Teaching Hospital, Abbottabad from jan 2023 to jan 2024. Patients ≥40 years, of either gender, with hepatic encephalopathy due to cirrhosis were included. Diagnosis and severity were assessed using the West-Haven classification. Intravenous branched chain amino acids were administered. Clinical response was recorded on the third day post-admission and stratified according to baseline demographics and disease severity.

Results: A total of 196 patients were enrolled, comprising 109 males (55.6%) and 87 females (44.4%). The mean age was 53.8 ± 10.2 years. Hepatotoxicity developed in 96 (49%) patients during treatment. Clinical efficacy of BCAAs showed no significant difference across age, gender, or baseline West-Haven grade. Statistical analysis revealed a p-value >0.05, indicating no significant therapeutic benefit. Although minor symptomatic improvements were observed

in some individuals, BCAAs did not provide consistent clinical outcomes. These findings suggest that branched chain amino acids may not play a definitive role in the management of hepatic encephalopathy due to liver cirrhosis.

Conclusion: This study concludes that intravenous branched chain amino acids do not significantly improve clinical outcomes in patients with hepatic encephalopathy secondary to cirrhosis of the liver. Their efficacy was not influenced by age, gender, or baseline severity of encephalopathy. Given the lack of statistical benefit, routine use of BCAAs for hepatic encephalopathy cannot be recommended. Larger, controlled trials are warranted to further clarify their role in management protocols.

Keywords: Hepatic Encephalopathy; Liver Cirrhosis; Branched Chain Amino Acids; West-Haven Classification

Introduction:

Hepatic encephalopathy (HE) is a serious neuropsychiatric complication of both acute and chronic liver disease. It is characterized by cognitive impairment, disorientation, altered consciousness, and in severe cases, coma. The pathophysiology of HE is complex, involving elevated blood ammonia levels, systemic inflammation, astrocytic swelling, and altered neurotransmission [1]. Ammonia, largely produced by gut bacteria, bypasses the diseased liver due to impaired detoxification and portosystemic shunting, crosses the blood-brain barrier, and disrupts cerebral function, leading to astrocytic edema and cerebral dysfunction [2].The prevalence of HE is high among patients with cirrhosis, and its incidence continues to increase in countries with a high burden of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, such as Pakistan [3]. A study in Jamshoro, Sindh, reported infection (67%), constipation (49%), and gastrointestinal bleeding (45%) as the most common precipitating factors for HE in cirrhotic patients, with high mortality in patients with grade IV encephalopathy [4]. Similarly, a study from Peshawar identified electrolyte imbalance (56%), diarrhea (40%), constipation (32%), and infection (24%) as important precipitating factors [5]. These findings highlight the multifactorial nature of HE in cirrhotic populations and underscore its high clinical significance. Traditionally, protein restriction was recommended in HE management, but this practice has largely been abandoned due to the adverse effects of protein malnutrition [6]. Current standard therapy emphasizes the identification and treatment of precipitating factors, with non-absorbable disaccharides such as lactulose and antibiotics like rifaximin serving as first-line therapies [7]. Other potential therapeutic options include benzodiazepine receptor antagonists, zinc supplementation, L-ornithine-L-aspartate, sodium benzoate, dopamine receptor agonists, probiotics, and branched chain amino acids (BCAAs) [8].BCAAs, consisting of leucine, isoleucine, and valine, are essential amino acids involved in nitrogen metabolism and protein synthesis. They may provide benefit in HE by facilitating ammonia detoxification, restoring plasma amino acid balance, and reducing the influx of aromatic amino acids into the brain [8]. However, their role remains controversial. Some studies suggest that BCAA supplementation improves minimal HE, muscle mass, and neurocognitive function [9], whereas others report no reduction in HE recurrence or mortality. Afzal et al. reported that BCAAs reversed HE in 52% of patients, suggesting a therapeutic benefit [10]. Another randomized controlled trial demonstrated reduced mortality and shorter hospital stay in patients receiving BCAAs compared with controls. Conversely, a multicenter randomized controlled trial involving 116 cirrhotic patients showed that BCAAs did not reduce

HE recurrence, though improvements in muscle mass and minimal HE was noted. Systematic reviews and meta-analyses have also reported mixed outcomes, with some studies indicating no significant benefit and others highlighting potential increased mortality with intravenous BCAAs [11]. Given the conflicting evidence, further research is warranted to clarify the clinical utility of BCAAs in cirrhotic patients with HE. This study was conducted to evaluate the efficacy of intravenous BCAAs in improving consciousness levels in patients with HE due to cirrhosis, and to determine their potential role in local treatment protocols.

Methods: A total of 196 patients were included using non-probability consecutive sampling. Patients aged 40 years or older, of either gender, with clinically diagnosed hepatic encephalopathy due to cirrhosis were enrolled. Diagnosis and severity were assessed according to the West-Haven classification. Intravenous BCAA supplementation was administered to all patients. Clinical response was recorded on the third day of admission and stratified according to baseline age, gender, and encephalopathy grade. Outcomes were compared, and statistical significance was assessed.

Inclusion Criteria:

Patients aged ≥40 years, of either gender, with cirrhosis of liver and hepatic encephalopathy diagnosed clinically and graded according to West-Haven classification were included in the study.

Exclusion Criteria:

Patients with hepatic encephalopathy due to non-cirrhotic causes, concomitant renal failure, recent use of psychoactive drugs, advanced malignancy, or non-compliance with therapy were excluded from the study.

Ethical Approval:

Ethical approval was obtained from the Institutional Review Board of Ayub Teaching Hospital, Abbottabad Written informed consent was obtained from patients or their attendants. Patient confidentiality was maintained throughout the study, and the research was conducted in accordance with the Declaration of Helsinki.

Data Collection:

Baseline demographic data, clinical features, and West-Haven grade were recorded at admission. Intravenous BCAAs were administered to all patients as per hospital protocol. Response was assessed on day three post-admission and documented in structured proformas. Patients were monitored for adverse outcomes, hepatotoxicity, and mortality during hospital stay.

Statistical Analysis:

Data were analyzed using SPSS version 24.0. Quantitative variables, such as age, were presented as mean ± standard deviation. Qualitative variables, including gender and treatment response, were presented as frequencies and percentages. The Chi-square test was used for categorical variables. A p-value <0.05 was considered statistically significant.

Results:

A total of 196 patients with hepatic encephalopathy secondary to cirrhosis were included in this study. Of these, 109 (55.6%) were male and 87 (44.4%) were female. The mean age was 53.8 ± 10.2 years. Hepatotoxicity developed in 96 (49%) patients during the study period. Stratification of BCAA efficacy across age groups, gender, and baseline West-Haven grade of encephalopathy demonstrated no statistically significant differences, with all comparisons

yielding p-values greater than 0.05.Although minor symptomatic improvement was noted in a subset of patients, particularly those with grade II encephalopathy, no consistent pattern of benefit was observed. Patients with advanced grades (III and IV) showed poor response, with high rates of morbidity and mortality. Overall, BCAA administration did not significantly alter hospital outcomes, nor did it reduce the progression of encephalopathy or in-hospital mortality. These findings suggest that intravenous BCAAs do not provide a meaningful therapeutic advantage in the management of HE secondary to cirrhosis.

Table 1: Demographic and Clinical Characteristics of Patients (n=196)

Characteristics	Frequency (n)	Percentage (%)
Total Patients	196	100
Male	109	55.6
Female	87	44.4
Mean Age (years)	53.8 ± 10.2	–
Hepatotoxicity	96	49.0

Table 2: Response to Branched Chain Amino Acids (BCAA) by Baseline Grade of Hepatic Encephalopathy

West-Haven Grade	Total Patients (n)	Response Observed (n, %)	p-value
Grade I	40	12 (30.0%)	>0.05
Grade II	76	20 (26.3%)	>0.05
Grade III	48	8 (16.7%)	>0.05
Grade IV	32	2 (6.3%)	>0.05

Table 3: Stratification of BCAA Efficacy by Age and Gender

Variables	Total (n)	Responders (n, %)	Non-Responders (n, %)	p-value
Age <50	82	18 (22.0%)	64 (78.0%)	>0.05
Age ≥50	114	24 (21.1%)	90 (78.9%)	>0.05
Male	109	24 (22.0%)	85 (78.0%)	>0.05
Female	87	18 (20.7%)	69 (79.3%)	>0.05

Table 4: Overall Clinical Outcomes in Patients Receiving BCAA

Outcomes	Frequency (n)	Percentage (%)
Symptomatic Improvement	42	21.4
No Improvement	154	78.6
Hepatotoxicity	96	49.0
Progression to Severe HE (Grade IV)	38	19.4
In-Hospital Mortality	32	16.3

Discussion:

Hepatic encephalopathy (HE) remains a significant cause of morbidity and mortality in patients with cirrhosis worldwide. The pathogenesis of HE is complex, involving hyperammonemia, neuroinflammation, astrocytic swelling, and altered neurotransmission. In this study, we evaluated the efficacy of branched chain amino acids (BCAAs) in patients with cirrhosis-

related HE. Our findings demonstrated no significant clinical benefit of intravenous BCAAs in improving consciousness levels or altering overall outcomes, with response rates not significantly associated with age, gender, or baseline West-Haven grade. These results are consistent with several previous studies that have questioned the therapeutic role of BCAAs in this setting. Earlier studies on BCAAs have produced mixed results. Afzal et al. reported a 52% reversal of HE with BCAA supplementation. Similarly, Malaguena et al. demonstrated improved outcomes, including reduced mortality and shorter hospital stay, in patients treated with BCAAs compared with standard therapy alone [12]. Marchesini et al. also noted benefits in minimal HE and muscle mass preservation, although recurrence rates of overt HE remained unchanged [13]. In contrast, meta-analyses have frequently failed to demonstrate consistent advantages, with Gluud et al. reporting no significant mortality or recurrence benefit, though a modest improvement in cognitive outcomes was observed [14]. Our findings align more closely with those large-scale analyses, suggesting that intravenous BCAAs may not provide significant clinical benefit in acute HE management. One possible explanation for this discrepancy lies in patient heterogeneity. Studies that demonstrated positive outcomes often included patients with minimal HE or chronic low-grade encephalopathy, where BCAA supplementation might restore amino acid balance and improve subtle neurocognitive deficits [15]. In contrast, our study population predominantly consisted of patients with advanced grades of encephalopathy, in whom astrocytic swelling and cerebral edema are already severe, limiting the potential impact of amino acid supplementation [16]. Recent literature also highlights the potential role of BCAAs in long-term outcomes rather than acute HE reversal. A Japanese cohort demonstrated improved survival in cirrhotic patients receiving oral BCAAs over prolonged periods, with benefits attributed to enhanced muscle protein synthesis and prevention of sarcopenia [17]. Sarcopenia, increasingly recognized as a prognostic factor in cirrhosis, may worsen HE by impairing ammonia detoxification via muscle metabolism [18]. Thus, BCAA supplementation might be more beneficial in chronic management and nutritional support rather than acute HE treatment. Another important consideration is the route and duration of BCAA therapy. Most randomized controlled trials evaluating oral BCAA supplementation reported modest benefits in quality of life and minimal HE, whereas intravenous administration has been less consistent [19]. The lack of standardized dosing regimens, variable treatment durations, and issues with patient compliance further complicate interpretation of outcomes. Our study, limited to short-term intravenous administration, may not capture potential longer-term benefits observed in chronic supplementation protocols [20]. Emerging therapeutic options also influence the relevance of BCAAs in HE management. Rifaximin, when combined with lactulose, has demonstrated robust evidence in reducing HE recurrence and improving hospitalization rates. Similarly, L-ornithine-L-aspartate (LOLA) has shown efficacy in lowering blood ammonia and improving cognitive function. Probiotics and fecal microbiota transplantation are gaining interest as methods to alter gut microbiota composition and reduce ammonia production[21-22]. In comparison, the evidence base for BCAAs remains weaker, with recent Cochrane reviews emphasizing the need for larger, high-quality randomized trials. Furthermore, the economic considerations of BCAA therapy cannot be ignored. In resource-limited healthcare systems, such as Pakistan, cost-effectiveness is crucial in guiding treatment choices. Oral or intravenous BCAA preparations are expensive, and given the lack of robust efficacy in acute HE, their routine use cannot be recommended.

Instead, prioritizing therapies with proven benefit, such as lactulose, rifaximin, and management of precipitating factors, remains the cornerstone of treatment[23-25].

Limitations:

The limitations of this study include its single-center design, relatively small sample size, and short duration of follow-up. Only short-term intravenous administration of BCAAs was evaluated, without comparison to oral formulations or prolonged therapy. Nutritional status and sarcopenia, which may influence outcomes, were not systematically assessed.

Conclusion:

This study demonstrates that intravenous branched chain amino acids do not significantly improve clinical outcomes in cirrhotic patients with hepatic encephalopathy. Their efficacy was not influenced by age, gender, or encephalopathy grade. Given the absence of statistical benefit, routine use of BCAAs in acute HE management cannot be recommended.

Future Directions:

Future studies should focus on identifying subgroups most likely to benefit from BCAA therapy, particularly patients with minimal HE or sarcopenia. Large, multicenter randomized trials with standardized dosing regimens and longer follow-up are needed. Exploring synergistic effects of BCAAs with other therapies may further clarify their clinical utility.

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Authors Contributions

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