Original Article

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Current Practice of Branched Chain Amino Acids Administration in Patients with Liver Cirrhosis: A Physician Survey

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ABSTRACT

Introduction: Protein Energy Malnutrition (PEM) is prevalent in about 65-90% of patients with liver disorders. PEM is usually associated with poor quality of life, high risk of complications, morbidity and mortality, and longer duration of hospital stays. PEM is also associated with decreased skeletal muscle mass and reduced levels of serum albumin and Branched Chain Amino Acids (BCAAs). Therefore, BCAAs are recommended as nutritional therapy in various liver disorders.

Aim: To understand the current practice of BCAA use in patients with liver cirrhosis in India.

Materials and Methods: A cross-sectional, questionnaire-based survey was conducted pan India involving 100 gastroenterologists over a period of four months from September 2019 to December 2019. Each physician participated in the survey after verbal consent. Ample time was given for completion of the questionnaires.

Results: Out of 83 participating physicians, nearly 3/4th considered liver cirrhosis as the most common Gastrointestinal (GI) disorder where nutrition is important in patient management. Malnutrition was commonly observed in patients with cirrhosis by nearly over 80% physicians and was most common in patients with decompensated cirrhosis. Weight loss and loss of appetite can be early signs of sarcopenia as these were common profiles observed in patients with malnutrition. Total 51.8% physicians considered BCAA administration in all Child-Pugh class patients. The practice of BCAA treatment with regards to its dose and duration highly varied for patients with cirrhosis, Hepatic Encephalopathy (HE), and Liver Transplantation (LT). Proteins from vegetarian source (50.6%) and BCAA supplementation (96.4%) were considered as major treatments for HE patients. Majority of the physicians reported that BCAA administration improved quality of life (52.4%), reduced HE episodes (49.4%), improved muscle mass (50%), and reduced hospitalisation rates (49.4%) in 20-40% of their patients. In all, 92.8% of physicians suggested that early administration of oral BCAA can prolong the waiting period for LT.

Conclusion: Branched Chain Amino Acids (BCAA) is an integral part of nutritional management in patients with liver cirrhosis in India. Further studies are required to guide the decision on dose and duration of BCAA treatment in the management of cirrhosis.

Keywords: Amino acid supplementation, Hepatic encephalopathy, Liver transplantation, Management

INTRODUCTION

Nutrition is an integral part of human health. It also plays an important role in various clinical disorders. In particular, nutrition is critical to the management of various GI disorders [1]. Considering the importance of nutrition in liver disorders, European Association for the Study of the Liver (EASL) guidelines were released in 2019, which provided insights on screening, assessment and principles of nutritional management. These guidelines provide recommendations for nutritional management in specific populations such as patients with HE or those undergoing LT [2]. It is emphasised that malnutrition in the form of sarcopenia is observed in nearly 20-50% of patients with compensated and decompensated liver cirrhosis, respectively [3].

Malnutrition also affects the Quality of Life (QoL) in these patients [4]. Thus, managing adequate nutritional requirements in liver cirrhosis is crucial. The EASL guidelines recommended use of BCAA and leucine-rich amino acids supplementation in patients with decompensated cirrhosis whose nitrogen intake is not adequately achieved with oral diet. Further, BCAA supplementation is recommended especially for patients with HE to improve neuropsychiatric performance [2]. Additionally, sarcopenia is identified as a predictor of mortality in liver cirrhosis, and supplementation with BCAA improved the survival in sarcopenic cirrhotic patients [5]. Evidence also indicates sarcopenia being a predictor of mortality in patients undergoing living donor LT [6]. These data indicate the importance of nutritional management in patients with liver cirrhosis.

Very few clinical studies have evaluated the role of nutritional therapy in patients with liver cirrhosis from India. A study by Maharshi S et al., observed improvement in QoL after nutritional therapy (30-35 kcal/kg/d, 1.0-1.5 g vegetable protein/kg/d) in cirrhotic patients with minimal HE [7]. However, published evidence pertaining to the role of BCAA in nutrition of cirrhotic patients is lacking. Additionally, there are no guidelines in India concerning the use of BCAA for liver cirrhosis. Thus, to understand the current practice of BCAA supplementation in patients with liver cirrhosis in the Indian setting, the present cross-sectional survey of physicians involved in the management of liver cirrhosis and LT was conducted.

MATERIALS AND METHODS

This cross-sectional questionnaire-based survey was conducted from September 2019 to December 2019 across India. The participating physicians were gastroenterologists who had immense experience in the management of liver cirrhosis. The study setting included hospitals and/or clinics of practicing gastroenterologists. Written informed consent was obtained from all survey participants, and physician confidentiality and anonymity were maintained throughout the study conduct. In accordance with local legislation and national guidelines, as this survey did not involve any intervention or direct participation of a patient, ethical approval by an independent ethics review board was not required.

Survey instrument: The survey instrument was a questionnaire designed to assess the current practice of BCAA use in management of liver cirrhosis. It consisted of 15 open and closed ended questions pertaining to various aspects of physician practice with respect to

BCAA use. The validated questionnaire (approval no. INDUSG193920) is shown in [Table/Fig-1]. Questions were pertinent to initiation of BCAA, dose, duration in different indications, and possible observed outcomes with BCAA use. All physicians who verbally consented for participation in the survey were given adequate time to respond to the questionnaire. Duly filled questionnaires were collected from the physicians.

Sr. No.	Questions
1.	Based on your clinical practice, which are the GI disorders where role of nutrition is most important?
2.	What is the prevalence of malnutrition in cirrhosis in your clinical practice?
3.	In your clinical practice, what percentage of patients you have observed suffering from compensated and decompensated cirrhosis to be associated with malnutrition and sarcopenia?
4.	Data indicates starvation is an important risk factor for sarcopenia in Indian cirrhotic patients. Can you please elaborate the profile of patients who present with sarcopenia/malnutrition in your clinical practice?
5.	It has been observed that early administration of oral BCAA can prolong the waiting period for liver transplantation by reserving hepatic reserve in cirrhotics. What is your opinion on the same?
6.	What in your opinion should be the daily recommended dose and duration of BCAA in the patients suffering from HE or cirrhosis, or awaiting liver transplant?
7.	In your clinical practice, when do you start BCAA in patients with decompensated cirrhosis?
8.	Could you elaborate on the place of therapy of BCAA depending on the grade/severity of cirrhosis, in your clinical practice (Child-Pugh A/B/C)?
9.	Do you believe Fischer ratio (BCAA:AAA) imbalance is a critical factor to treat in HE patients? Please elaborate.
10.	What treatment option are you using to correct Fischer ratio in patients with HE? [dietary protein (vegetative or non vegetative)/protein supplementation/BCAA supplementation/other]
11.	What is major indicator to assess the efficacy of BCAA therapy in cirrhosis/HE/liver transplantation (quality of life/HE episodes in year/ muscle mass increase/ reduced hospital admission rates)
12.	What is the percentage of patient on BCAA therapy that have demonstrated improvements in quality of life?
13.	What is the percentage of patients on BCAA therapy that have demonstrated improvements in HE episodes in a year?
14.	What is the percentage of patients on BCAA therapy that have demonstrated improvements in muscle mass increase?
15.	What is the percentage of patients on BCAA therapy that have demonstrated improvements in reducing hospital admission rates?

[Table/Fig-1]: Questionnaire (BCAA).
AAA: Aromatic amino acid; BCAA: Branched chain amino acid; HE: Hepatic encephalopathy

STATISTICAL ANALYSIS

Data from the questionnaire were entered and analysed using Microsoft Excel. Proportion of physicians responding to each question were determined. Data were presented as frequency and percentages for each question.

RESULTS

Across India, 100 gastroenterologists were approached, out of which 83 provided informed consent and provided responses to all the survey questions. Liver cirrhosis was considered to be the most common GI disorder where nutrition was observed to play an important role. It was the first choice of 3/4th of the participants across various disorders. Following liver cirrhosis, chronic pancreatitis, inflammatory bowel disease, and non alcoholic fatty liver disease, in that order, were considered to be conditions where nutrition played an important role in disease management [Table/Fig-2].

Total, 63 (75.9%) and 61 (73.5%) physicians responded for the question of number of patients sufferring from malnutrition and sarcopenia in decompensated and compensated cirrhosis respectively. Over 50% of physicians reported that >60% of the patients with decompensated cirrhosis suffer from malnutrition, whereas n=61 physicians reported that <40% of patients with compensated cirrhosis have malnutrition in routine practice [Table/Fig-3].

Categories	First choice	Second choice	Third choice	Fourth choice	Fifth choice
Liver cirrhosis (n=83)	63 (75.9)	7 (8.4)	6 (7.2)	2 (2.4)	5 (6.0)
Chronic pancreatitis and PEI (n=68)	7 (10.3)	26 (38.2)	19 (27.9)	10 (14.7)	6 (8.8)
IBD (n=65)	9 (13.8)	10 (13.5)	29 (44.6)	12 (18.5)	5 (7.7)
NAFLD (n=74)	16 (21.6)	17 (23.0)	13 (17.6)	26 (35.1)	2 (2.7)
IBS (n=63)	4 (6.3)	5 (7.9)	2 (3.2)	8 (12.4)	44 (69.8)

[Table/Fig-2]: Gastrointestinal disorders where nutrition is most important.
IBD: Inflammatory bowel disease; IBS: Irritable bowel syndrome; NAFLD: Non-alcoholic fatty liver disease; PEI: pancreatic exocrine insufficiency

Percentage	Decompensated cirrhosis (n=63)	Compensated cirrhosis (n=61)
≤20%	6 (9.5)	21 (34.4)
21%-40%	15 (23.8)	23 (37.7)
41%-60%	9 (14.3)	12 (19.7)
61%-80%	22 (35)	5 (8.2)
>80%	11 (17.4)	0

[Table/Fig-3]: Proportion of patients as per type of cirrhosis that suffer from malnutrition and sarcopenia.

Among patients presenting with sarcopenia/malnutrition, unintentional weight loss of >6 kg in the last 6 months and decreased appetite over the last month were observed as common presentations by 55.4% and 42.2% physicians, respectively. Moreover, 27.7% physicians reported unintentional weight loss of >3 kg in the last month as one of the presentations [Table/Fig-4].

Patients with sarcopenia/malnutrition	n	%
Lost unintentional weight of more than 6 kg in the last 6 months	46	55.4
Lost unintentional weight of more than 3 kg in the last month	23	27.7
Patients experiencing a decreased appetite over the last month	35	42.2
Patients using supplemental drinks or tube feeding over the last month	3	3.6

[Table/Fig-4]: Profile of patients presenting with sarcopenia/malnutrition.

When considering BCAA administration per Child-Pugh grading, 51.8% physicians considered all grades (A, B, and C) for BCAA use in patients with cirrhosis, whereas 44.6% considered BCAA use only in patients with grades B and C [Table/Fig-5].

Categories	n	%
Child-Pugh A	0	0
Child-Pugh B	0	0
Child-Pugh C	3	3.6
All of the above	43	51.8
Child-Pugh B and C	37	44.6

[Table/Fig-5]: Branched-chain amino acid administration depending on the grade/ severity of cirrhosis.

Majority of physicians (71.1%) considered serum albumin ≤3.5 gm/dL as common indication for BCAA initiation in decompensated cirrhosis. This was followed by BCAA to tyrosine ratio (BTR) ≤3.5, which was considered by 37.3% physicians. Other indications included prothrombin activity ≤60% and platelet count of ≤100 000/mm^3 by nearly equal number of participants [Table/Fig-6].

Categories	n	%
Serum albumin ≤3.5 gm/dL	59	71.1
BTR ≤3.5	31	37.3
Prothrombin activity ≤60%	14	16.9
Platelet count ≤100000/mm^3	12	14.5

[Table/Fig-6]: Indication to start branched-chain amino acid in patients of decompensated cirrhosis.
BCAA: Branched-chain amino acid; BTR: BCAA to tyrosine ratio

Dose and duration of BCAA treatment for patients with cirrhosis, HE and patients listed or undergoing LT are shown in [Table/Fig-7]. With regards to the dose and duration of BCCA treatment in different liver conditions, we received 69 (83.1%) and 64 (77.1%) physicians responses, respectively. For patients with cirrhosis, dose varied among the physicians, with 21.7% recommended doses ≤10 gm/day and 23.2% recommended doses >10 gm/day. Frequency was predominantly twice a day as stated by 55.1% of physicians. The duration was considered to be ≤3 months by 43.6% of physicians, whereas 29.7% considered duration to be ≥6 months. Some suggested continuation over long-term or until transplantation.

Cirrhosis					
Dose (n=69)	**n**	**%**	**Duration (n=64)**	**n**	**%**
≤10 gm/day	15	21.7	≤3 months	28	43.6
>10 gm/day	16	23.2	3-6 months	4	6.3
OD	2	3.0	≥6 months	19	29.7
BD	38	55.1	Continue/long-term	4	6.3
BD or TID	2	3.0	Till transplantation	6	9.4
TID	2	3.0	Intermediate	2	3.1
			Depends	1	1.6
HE					
Dose (n=69)	**n**	**%**	**Duration (n=64)**	**n**	**%**
≤10 gm/day	15	21.4	≤3 months	40	61.5
>10 gm/day	11	15.7	3-6 months	2	3.1
OD	1	1.4	≥6 months	12	18.5
BD	34	48.6	Continue	3	4.6
TID	14	20.0	Life long	1	1.5
			Till transplantation	4	6.2
			Till recovery	1	1.5
			Titrate	2	3.1
Liver transplant					
Dose (n=69)	**n**	**%**	**Duration (n=64)**	**n**	**%**
≤10 gm/day	6	14.6	≤3 months	8	19.5
>10 gm/day	6	14.6	3-6 months	1	2.4
BD	16	39.0	≥6 months	13	31.7
BD or TID	1	2.4	Before transplant	1	2.4
TID	9	22.0	Peri-transplant x 6-8 weeks	1	2.4
QID	3	7.3	Till transplantation	13	31.7
			Depends	1	2.4
			Lifetime	1	2.4
			Not required	2	3.1

[Table/Fig-7]: Dose and duration of branched-chain amino acid practiced in different liver conditions.
BCAA: Branched-chain amino acid; BID: Twice a day; QD: Once a day; QID: Four times a day; TID: Thrice a day; HE: Hepatic Encephalopathy; Total 69 physicians responded with regards to dose and 64 physicians respondend in regards to duration of BCCA treatment in different liver conditions

For patients with HE, doses of ≤10 gm/day and >10 gm/day were stated by 21.4% and 15.7% of the physicians, respectively. Frequency was predominantly twice a day as stated by 48.6% of physicians. Majority (61.5%) recommended treatment duration of ≤3 months, whereas 18.5% recommended duration of >6 months. In all, 6.2% of physicians were of the opinion that BCAA should be continued until transplantation.

For patients on the waiting list or those undergoing LT, lower number physicians (n=41) commented on dose and duration of BCAA treatment. The number of physicians choosing doses of ≤10 gm/day or >10 gm/day was similar. In total, 39% and 22% of physicians recommended twice a day or thrice a day dosing, and a few suggested BCAA use four times a day. Nearly one third (31.7%) physicians considered duration of therapy to be >6 months or until transplantation.

For management of HE, 94% of physicians considered Fischer ratio imbalance to be a critical factor. As high as 96.4% considered BCAA administration as a treatment option, whereas 50.6% physicians considered dietary vegetarian protein source as essential. The combination of vegetarian source of dietary protein and BCAA together was most preferred combination (48.2%) as shown in [Table/Fig-8].

Categories	n	%
a) Dietary protein (vegetative) intake	42	50.6
b) Dietary protein (non vegetative) intake	3	3.6
c) Protein supplementation	26	31.3
d) BCAA supplementation	80	96.4
e) Other	3	3.6
a+b	2	2.4
a+c	21	25.3
a+d	40	48.2
c+d	24	28.9

[Table/Fig-8]: Treatment options to correct Fischer ratio in patients with hepatic encephalopathy.
BCAA: Branched-chain amino acid

Improving muscle mass, reducing HE episodes and improving QoL were considered to be the indicators for assessing BCAA efficacy in patients with cirrhosis or HE or those undergoing LT. In routine practice, nearly half of the participating physicians observed that 20%-40% of their patients showed improvement in QoL (52.4%), reduction in HE episodes (49.4%), increase in muscle mass and reduction in hospitalisation rates (49.4%). Furthermore, nearly one third observed improved QoL, reduced HE episodes and increased muscle mass in 40%-60% of their patients, whereas nearly one-fourth of physicians observed reduction in hospitalisation rates in 40%-60% of patients.

As high as 92.8% physicians considered that early administration of oral BCAA can prolong the waiting period for LT.

DISCUSSION

Nutrition is one of the important management aspects for patients with liver cirrhosis. EASL guidelines have specified nutrition recommendation for these patients [2]. BCAA is an important nutrition therapy for management of liver cirrhosis. In liver disorders, BCAA acts via multiple mechanisms. It has shown to induce mitochondrial biogenesis, inhibit reactive oxygen species production, stimulate albumin and glycogen synthesis, inhibit hepatocyte apoptosis and promote hepatocyte regeneration, stimulate hepatocyte growth factors, improve insulin resistance, as well as induce dendritic cell maturation [8]. As malnutrition is more common in decompensated cirrhosis as observed from this survey and from previous reports, it needs attention [3]. Though quantitative methods such as computed tomography-based assessment of muscle mass are best for screening and detecting sarcopenia, these may not be feasible in all patients in routine clinical practice [2].

Alternatively, body mass assessment using anthropometric measures can be used to determine sarcopenia [2]. In clinical practice, physicians considered that unintentional weight loss of >6 kg in the last 6 months can be one of the indicators of sarcopenia. Also, changes in diet as assessed from dietary interviews can be another indicator. Authors have observed that atleast 42.2% of physicians considered weight loss or decreased appetite over the last month as one of the presentations in patients with sarcopenia. EASL guidelines recommend assessment of dietary intake by trained personnel in terms of quality and quantity of food and supplements, fluids, sodium in diet, number and timing of meals during the day and barriers to eating in sarcopenia [2].

Severity of liver cirrhosis is graded by using Child-Pugh criteria. A total of 51.8% physicians suggested use of BCAA despite severity of disease whereas 44.6% considered its use in grades B and C only. A study by Habu D et al., observed that BCAA administration was able to maintain serum albumin for two years in both compensated as well as decompensated cirrhosis [9]. Another study by Nishiguchi S and Habu D identified that early administration of BCAA in cirrhosis with Child-Pugh classes A and B can help achieve better prognosis and maintain QoL [10]. Evidence also indicates that BCAA administration in early disease is associated with increasing total hepatic parenchymal cell mass [8]. These data indicate that BCAA supplementation should be done irrespective of the severity of cirrhosis. This was practiced by nearly half of all the physicians in the survey. Majority of the physicians considered hypoalbuminemia followed by BTR as indicators to initiate BCAA in decompensated cirrhosis. However, it should be noted that in patients with malnutrition, BTR declines before the reduction in serum albumin is evident, thereby indicating that BTR is a useful tool to decide appropriate time for the use of BCAA [11].

The duration and dose of BCAA for cirrhosis and its complications may vary in different parts of the world. In present survey it was found that there are varying doses and duration of treatment with BCAA in patients with liver cirrhosis, HE as well as in patients with LT. EASL guidelines identify that long-term supplementation of oral BCAA may be of better nutritional value [2]. In a study by Park JG et al., BCAA (12.45 g) administration daily for atleast six months was associated with significant improvement in model for end-stage liver disease score in patients with advanced cirrhosis [12]. Another study in patients with decompensated cirrhosis, orally administered BCAA at 12 gm/day for two years resulted in improved event-free survival, serum albumin concentration, and QoL [13]. An Italian study in patients with liver cirrhosis reported improvement in both the serum bilirubin levels and Child-Pugh scores with long-term (one year) BCAA supplementation [14]. In patients with decompensated cirrhosis, oral BCAA at 12 gm/day for two years resulted in reduction in the risk of HE [15]. These evidences indicate that BCAA should be administered for atleast six months or more to attain beneficial effects in patients with cirrhosis.

During the treatment with BCAA, Fischer ratio is critical to the management of HE as was agreed by 94% of physicians. Amino acid imbalance becomes more marked with increasing severity of liver disease. A lower Fischer ratio is associated with HE [8]. In managing HE, oral dietary protein intake is preferred as indicated in the EASL guidelines. BCAA supplementation is necessary in all HE patients to improve neuropsychiatric performance and to reach the recommended nitrogen intake [2]. This was evident in the survey where dietary protein intake and BCAA both were preferred by majority of the physicians. Preference was given to proteins from vegetarian sources because it has shown to be associated with significantly better nitrogen balance in patients with HE [16].

In assessing the efficacy of BCAA, QoL, frequency of HE episodes, and increase in muscle mass were major indicators. Also, majority of the physicians suggested that 20% to 60% of patients with cirrhosis demonstrate positive impact on these outcomes, including reduced rates of hospitalisation. Evidence from clinical studies indicate that BCAA supplementation is associated with improved QoL [17], reduced hospitalisation rates [14], and improvement in minimal HE and muscle mass [18].

Studies also indicate that BCAA supplementation significantly lowers the composite outcome of all cause mortality, development of liver cancer, rupture of oesophageal varices, or progress of hepatic failure and therefore prolongs event-free survival [13]. In addition, majority of physicians suggested that BCAA administration prolonged the LT waiting period. A study by Kawamura E et al., reported that early interventional oral BCAAs might prolong the LT waiting period because of preservation of hepatic reserve in patients with cirrhosis [19]. However, further research is needed to substantially establish the role of BCAA in patients undergoing LT.

Limitations(s)

Although attempts were made to enrol participating gastroenterologists across India to reflect clinical practice pan India, the relatively low sample size and chances of recall bias among the physicians limit the generalisability of the survey findings. Future prospective studies with larger sample sizes and robust design are therefore warranted.

CONCLUSION(S)

In this first of its kind survey among physicians in India, which assessed the practice of oral BCAA supplementation in patients with liver cirrhosis, majority of the physicians considered nutrition as a critical part of patient management and recommended BCAA use irrespective of disease severity. Though dose and duration of BCAA varied among the participating physicians, they emphasised the need for long-term administration for atleast six months or beyond to achieve better clinical outcomes. Dietary vegetarian proteins along with BCAA supplementation were considered advisable in patients with HE. BCAA administration can improve the quality of life and muscle mass, reduced hospitalisation rates in cirrhotic patients, and could prolong the waiting time for LT.

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