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# Role of Branched Chain Amino Acids in the Management of Hepatic Encephalopathy

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**Abstract:** To know the association of branched chain amino acids (BCAA) in the management of hepatic encephalopathy. Prospective, comparative, non randomized open study. This study was conducted in Medical Unit-4, LUMHS, Hyderabad, Pakistan from January 2007to October 2007 in indoor patients. Forty Eight (48) cases of chronic hepatic encephalopathy were included for the study.24 patients were kept on branch chain amino acids and 24 patients were on control group. All investigations were done in all cases for the diagnosis and the classification of Chronic Liver Diseases (CLD) including ammonia and serum albumin level. Serum Ammonia and serum albumin level on admission day and sixth day and after four months were done. Recovery and reoccurrence of hepatic encephalopathy were compared on patients who were on brand chain amino acids given initially intravenously then kept on oral amino acids with those of control group without aminoleban. Those who were on aminoleban showed early improvement and recovery from hepatic encephapathy and subsequently on follow up visits at four months. Ammonia level which was initially raised decreased subsequently on sixth day and on fouth month. And their albumin level also increased at four month follow up compared to patients who did not received aminoleban. On grounds of above study we recommended branched amino acids for the treatment and prevention of chronic hepatic encephalopathy.

**Key words:** Hepatic Encephalopathy % Chronic Liver Disease % Aminoleban % Branched chain Amino Acids

## INTRODUCTION

The Major mechanism of hepatic encephalopathy due to liver cirrhosis currently attracting involves the intoxication and neurotransmitter theories [1,2]. The representative agents of intoxication are ammonia, methanethiol, phenol and short chain fatty acids. The neurotransmitter theory can be divided into the following two categories depending upon the types of amino acids as the amino acid-neurotransmitter theory and gamma aminobutyric (GABA) theory [3,4]. Fischer and Baldessarini, proponents of the amino acid – neurotransmitter theory. In patients suffering from hepatic encephalopathy plasma concentration of aromatic amino acids (AAA) such as phenylalanine, tyrosine and free tryptophan, as well as methionine, aspartic acid and glutamic acid are elevated where as branched amino acids (BCAA's) such as leucine, isoleucine and valine are decreased [5]. These researchers suggested that the condition would be improved if the plasma amino acids were normalized [6]. They then developed an amino acid solution (Fischer's solution) enriched in BCAA's and low in amino acids as a preparation of treating hepatic encephalopathy[7].

Severe HE may be reversed by a nutritional approach based on the administration of consistent amount of BCAA [1].

Malnutrition is a common feature of chronic liver failure CLF. Nutrient requirement is increased because of presence of a hypercatabolic state [2]. moreover food digestion and the absorption are often incomplete [3].

The increased muscle protein degradation coupled with impaired liver function induces a profound alteration of the plasma AA pattern characterized by an elevation in aromatic amino acid AAA phenylalanine (PHE), tyrosine (TYR) and tryptophan (TRP) and a reduction in branched amino acids AA (BCAA), valine (VAL), leucine (LEU) and isoleucine (ILEU) level [18]. These changes in the plasma AA profile very likely play a key role in the pathogenesis of HE and may therefore be responsible for the protein intolerance seen in CLF patients [19]. Plasma and brain accumulation of AAA may in fact cause a severe impairment of brain neurotransmitter synthesis, in turn causing HE [20,21]. The decrease in plasma BCAA, which

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compete with AAA for the blood brain transport [22], contributes greatly to the accumulation of AAA in the brain [17]. Fischer and colleagues have proposed an AAA mixture.

BCAA are metabolically very active. In the peripheral tissues they may be oxidized to produce energy [24] or may be act as antictabolic factors (particularly leucine) by stimulating the synthesis and reducing the degradation of muscle protein [25,26]. Indeed, in patients with chronic liver failure (CLF) i.v. BCAA decrease AA and ammonia plasma concentrations [27]. BCAA, by competing with AAA for blood brain transport [22], may reduce brain entry of AAA.

Since the first report by Fischer et al [22] a large number of aneedotal studies have been carried out which clearly show that severe HE may rapidly reversed by the i.v. administration of AA mixtures enriched with BCAA [29,33]. These findings have been subsequently confirmed by at least 5 randomized, controlled trials [34].

## PATIENTS AND METHODS

The patients with decompensated Liver cirrhosis (LC), who met the following study criteria were enrolled in the patient study.:All the cases of hepatic encephalopathy Grade II coma or a history of hepatic encephalopathy having HBV and HCV. Both males and females were enrolled. Before the start of the study an informed consent was obtained from the patients.

Out of 48 patients enrolled, they were divided into two groups Group-1 and Group 2, 24 patients were kept in each group. Group 1(24 patients) were kept on conventional treatment and Group 2 received both conventional as well as branched chain amino acids.In Group 1 kept on conventional therapy, out of 24 patients, 17 were males 7 were females and in Group 2 on conventional as well as on BCAA out of 24 patients, 17 were males and 07 were females. As for age distribution is concerned again they were divided into two groups. 1 and 2, Group 1 on conventional therapy were kept as under: 10 patients from age 30-39 12 from 40-49. while in 2 were chosen over 50 years of age.# In Group 2, who were kept on BCAA as well as conventional therapy their ages and numbers are: from 30-39 10 patients. 40-49 were 12 in numbers and patients above 50 years of age were 2 in number The above 48 patients were diagnosed on the bases of clinical history / examination / laboratory parameters including prothrombin time, serum albumin and serum ammonia level.

In both groups i.e. group I on conventional therapy and group II on conventional as well as on BCCA,their status regarding prothombin time, Albumin level and serum ammonia level in patients were as follows:

The difference of Prothrombin time in 8 patients was 3 to 6 seconds from control where as > 6 seconds in 6 patients were noted in each group.In both group out of 24 patients S. albumin level was <2.8mg/dl seen in 16 patients and S. albumin level between 2.8 and 3.1mg/dl were noted in remaining 6 patients. S. albumin and S. ammonia level were done on admission day, on $6^{th}$ day and at 4 months in both groups.

**Data Analysis:** The data were evaluated in SPSS version 16.0 the Fisher's exact and Pearson's chi-square test was applied among the categorical variable and independent samples T test was applied to compare the means among continuous variable. The p value < 0.05 was considered as statically significant level.

## RESULTS

Recovery and recurrence of hepatic encephalopathy were compared on patients who were on BCAA given initially intravenously than orally with those of group without BCAA. Those who were on BCAA showed early improvement and recovery and subsequently on follow up visits at four months. They not only showed improvement as for as their ammonia level is concerned which was initially raised but ammonia level decreased subsequently at $6^{th}$ day and on four month follow up. Their albumin level also increased from their initial reading noticed at four months follow up, compared to patients who did not received BCAA. Patients in group-2 was ion BCAA showed early improvement and recovery and subsequently on follow up visit at four months.Patients on BCAA showed improvement which initially without BCAA was raised but on sixth day and four months follow up it reduced significantly. Albumin level which was initially low either remain stabilized or in few patients it also raised. The mortality rate in group 2 patients compared to group 1 was also significantly low.

The results are as follows, In first week hospital stay in group I patients in comparison to group II patients was more than seven days (group 1 = 8 patients 33.3% and group 2 = 0 patients). P value < 0.001. 8 patients from group 2 remained hospitalized for 14 days while only one patient remain in hospital for 14 days (group 2 = 1 patient {14.2%} and in group 1 {33.3%}). Those who remained

more than 14 days were 16 from group 1 (66.7%) and 6 from group 2 (25.0%). The P value < 0.001 which is significant.

As for as serum ammonia level is concerned in group 1 on conventional therapy it was raised to 110.8 +/- 7.89, on sixth day 70.4 +/- 13.90 and at 4 months 50.080 +/- 8.58. While in group 2 on BCAA initially it was 120.5 +/- 19.75, On sixth day 50.8 +/- 8.16 on 4 months 20.583 +/- 3.855, with P value < 0.001 which is higly significant. Serum Albumin level initially in 16 patients from group 1 and from group 2 was < 2.8 (66.7%) in each group and in 8 patients it remain more than 2.8 to 3.1 i.e. 33.3% in each group. However in patients on BCAA either it remain near 3.1 or slightly raised at 4 months. Mortality in group 2 compared to group 1 was significantly decreased. Alive group 1 = 3 (12.5%) and in group 2 = 10 (41.9%) P value <0.04. Patients died from group 1 = 21 patients (67.5%) while in group 2 = 14 patients died (58.3%) P value <0.04 which is significant.

## DISCUSSION

Protein energy malnutrition (PEM) is a common manifestation in cirrhotic patients with reported incidences as high as 65-90%. In cirrhosis, protein malnutrition is usually represented by reduced serum albumin level and by decreased skeletal muscle volume (muscular protein). PEM affects largely the outcome of patients by determining both their quality of life and survival. As an intervention for energy malnutrition, frequent meal or late evening snack has recently been recommended [11,13]. Patients with low plasma BCAA have low serum albumin levels and those with high BCAA have high albumin [5]. Hyperammonemia is a common manifestation of cirrhotic patients due to impaired hepatic capacity to detoxicated ammonia. Instead, skeletal muscles and, to a lesser extent the brain clear blood ammonia by incorporating ammonia in the process of glutamine production from glutamate. The precursor glutamine requires BCAA for its synthesis. Thus, when exposed to hyperammonemia, skeletal muscle take up BCAA from the plasma to enhance their ability to degrade ammonia [16]. In contrast, cirrhotic patients lose hepatic storage of glycogen due to liver atrophy and also get resistant to insulin in their peripheral tissues. Majority of such BCAA oxidation is supposed to occur in skeletal muscles and contribute to enhanced uptake of BCAA from plasma by skeletal muscles [17].

Recent interests focused on the timing of administration of BCAA since day time BCAA is usually consumed by energy generation for physical exercise of skeletal muscle in liver cirrhosis. Nocturnal BCAA seem to be more favorable as source of protein synthesis by giving higher nitrogen balance [22]. Abnormal amino acids metabolism in Liver cirrhosis (LC) can be characterized by decreased concentration of BCAA and increased concentration of aromatic amino acids (AAA). In hepatic failure, the metabolism of AAA's and methionine is lowered, leading to elevated concentrations in the blood [16]. In contrast in the muscles the catabolism of BCAA's is accelerated, resulting in a decrease in the concentration of BCAA's [5.] Consequently, Fischer's ratio diminishes and the uptake of AA increased into brain [6,7]. This increased uptake leads to an increase in number of neurotransmitters causing encephalopathy. The AA solution that was developed by Fischer and Baldessarini 1 for the purpose of normalizing the amino acid balance can bring about a rapid symptomatic improvement in patients. The solution has been widely used in the treatment of hepatic failure [9,12]. Administration is restricted only to intravenous infusion, however, which limits the patients can be treated predominantly in patients. Such intravenous infusion are inconvenient for the patient with mild and moderate encephalopathy, [8,9,17]. In our study, long term clinical experiments was designed so that the uselessness of aminoleban in treating patients with hepatic failure can be identified more clearly. The neuropsychic symptoms and performance status also improved significantly in patients. Many patients were eventually able to undertake normal daily life without assistance. This may represent an improvement in the quality of life. The prognosis of LC is dependent on various factors such as total bilirubin and albumin in the serum, ascites and encephalopathy as well as nutritional condition [18].Malnutrition has been reported to be one of the major risk factors responsible for the death due to hepatic failure [19,20]. The patients receiving aminoleban EN were still alive at the end of 6-months study period. Consequently Aminoleban EN was considered to be effective in prolonging the life span of patients with decompensated LC. BCAA are known for their use an energy source. They also compete for entry across the blood brain barrier [21] with neutral amino acids that are precursors of monoamines [22], act as detoxicants for ammonia and accelerated protein synthesis in muscle while inhibiting the break down of

Table 1: Demographic profile of the patients (n = 48)

| | |
|---|---|
| Age (in years), Mean±SD (Range) | 41.2±7.2(30 – 55) |
| Gender: | |
| Male | 34(70.8%) |
| Female | 14(29.2%) |
| Age distribution: | |
| 30 to 39 | 20(41.6%) |
| 40 to 49 | 24(50%) |
| 50 and above | 4(8.4%) |

Table 2: Investigations of the patients done during their hospital stay and follow up

| | | | |
|---|---|---|---|
| Prothrombine Time | | | |
| 3 to 6 | 18(75.0%) | 18(75.0%) | NS |
| > 6 | 6(25.0%) | 6(25.0%) | |
| Serum Albumin | | | |
| < 2.8 | 16(66.7%) | 16(66.7%) | NS |
| 2.8 to 3.1 | 8(33.3%) | 8(33.3%) | |

Table 3: Hospital stay, mortality and observations

| Parameter | Group 1 Conventional treatment (n = 24) | Group II Conventional treatment & BCAA (n = 24) | P value |
|---|---|---|---|
| Hospital stay: | | | |
| 1 to 7 days | 0 | 8(33.3%) | < 0.001* |
| 8 to 14 days | 8(33.3%) | 1(4.2%) | |
| > 14 days | 16(66.7%) | 6(25.0%) | |
| Mortality: | | | |
| Alive | 3(12.5%) | 10(41.7%) | 0.04 |
| Dead | 21(87.5%) | 14(58.3%) | |
| Recurrence of Hepatic Coma (observed during 4 months) | | | |
| Up to 4 times | 3(12.5%) | 0 | |
| Up to 3 times | 6(25.0%) | 2(8.3%) | |
| Upto 2 times | 9(37.5%) | 3(12.5%) | |
| One time | 2(8.3%) | 2(8.3%) | |
| Nil | 4(16.7%) | 17(70.8%) | 0.003 |

* *P* value is statistically highly significant

Table 4: Serum Ammonia level of patients

| Parameter | Group 1 Conventional treatment (n = 24) | Group II Conventional treatment & BCAA (n = 24) | P value |
|---|---|---|---|
| Serum ammonia level: | | | |
| Initial | 110.8 ± 7.89 | 120.5 ± 19.75 | 0.03 |
| On 6$^{th}$ Day | 70.4 ± 13.90 | 50.8 ± 8.16 | < 0.001* |
| On 4 months | 50.080 ± 8.5800 | 20.583 ± 3.8551 | < 0.001* |

Results are expressed as Mean ± Standard Deviation

* *P* value is statistically highly significant

muscular protein. In conclusion, long term administration of the enteral amino acid nutrient, aminoleban EN, led to nutritional improvement with little adverse reactions as well as the improvement of the quality of life and performance status. Aminoleba EN was thus able to prolong the life span of patients with decompensated LC.

## CONCLUSION

In advanced liver cirrhosis long term nutritional supplements with oral BCAA is useful to prevent progressive hepatic failure and improves surrogate markers and health status. It also raises plasma albumin level, improves quality of life of patient and decrease incidence of subsequent hepatic encephalopathy in these patients. From our study it is observed that nutritional factor plays a significant role both in the pathogenesis as well as management of hepatic encephalopathy. The administration of solution rich in BCAA leads to mental recovery from acute hepatic encephalopathy in patients with liver cirrhosis.

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