ORIGINAL ARTICLE (APMC – 378) DOI: 10.29054/APMC/17.378

Role of Branched Chain Amino Acids in Hepatic Encephalopathy

Umair Ahmed, Aamir Shaukat, Hooria Aamir, Awais Ahmed

ABSTRACT

Introduction: Hepatic encephalopathy (HE) or portosystemic encephalopathy is a state characterized by disordered central nervous system functions because of failure of liver to detoxify nitrogenous agents originating from gut because of dysfunction of hepatocytes and portosystemic shunting. Patients with HE often present alteration of mental status varying from minor psychological abnormalities to deep coma. Multiple studies conducted worldwide suggest that the branched-chain amino acids (BCAAs) leucine, isoleucine, and valine may be useful in improving survival and reducing morbidity in patients with HE. **Objectives:** To compare the efficacy of branched chain amino acids in reversal of hepatic encephalopathy in patients with cirrhosis of liver with placebo. **Study Design:** Randomized control trial **Setting:** Medical Unit V, DHQ Hospital Faisalabad **Duration:** Study was carried out over a period of 6 months from 1st July 2016 to 30 December 2016 **Results:** A total of 60 patients (30 in each group) were enrolled, majority of the patients were between 41-50 years in both groups, 36.67% (n=11) in Study and 43.33% (n=13) control group, mean and standard deviation of age was calculated as 43.56±5.21 in study and 45.78±4.98 years in control group, 70% (n=21)patients were male in study group and 63.33% (n=19) in the control group, 30% (n=9) patients in study group and 36.67% (n=11) in control group were females, comparison of efficacy of BCAAs in reversal of HE with placebo reveals 63.33% (n=19) patients in study group showed reversal of HE and 26.67% (n=8) patients in control group**. Conclusion:** The results of the study conclude that branched chain amino acids are significantly effective in reversal of hepatic encephalopathy when compared with placebo.

Keywords: Hepatic encephalopathy, Comparison, Branched Chain Amino Acids, Efficacy

Corresponding Author
Dr. Umair Ahmed
Assistant Professor, Medicine
FMU/Allied Hospital, Faisalabad.
Contact: +92 300-9669550
Email: dr.umairahmed123@gmail.com

Submitted for Publication: 02-08-2017 *Accepted for Publication: 19-09-2017*

Article Citation: Ahmed U, Shaukat A, Aamir H, Ahmed A. Role of Branched Chain Amino Acids in Hepatic Encephalopathy. APMC 2017;11(4):267-71.

INTRODUCTION

Hepatic encephalopathy (HE) or portosystemic encephalopathy is a state characterized by disordered central nervous system functions because of failure of liver to detoxify noxious agents originating from gut because of dysfunction of hepatocytes and portosystemic shunting. The clinical spectrum of HE ranges from reversal of sleep pattern and mild intellectual impairment to deep coma.[1]Multiple Studies conducted worldwide have shown that overt HE affects 30 to 45% of patients with cirrhosis of liver and an even greater number of patients may be suffering with minimal degree of encephalopathy.[2,3] In cirrhosis of liver, the portal blood bypasses the liver via potosystemic shunts because of increased hepatic resistance due to fibrosis, and neuro-toxic metabolites like ammonia, free fatty acids and mercaptans pass directly to the brain via systemic circulation to produce HE. Ammonia induced alteration of brain neurotransmitter balance especially at asterocye-neuron interface is believed to be an important pathological mechanism. Besides these hemodynamic alterations, the effective hepatocyte mass is greatly reduced in cirrhosis, therefore liver is unable to detoxify even small amounts of neuro-toxins.[1]

The three-branched chain amino acids (BCAAs), valine, leucine and isoleucine are included in the nine essential amino acids needed for humans. In patients with advanced liver cirrhosis, serum concentration of these BCAAs is decreased, while the concentrations of the aromatic amino acids (AAAs) which include phenylalanine and tyrosine is increased, resulting in a low ratio of BCAAs to AAAs, a ratio known as the Fischer ratio. A decreased Fischer ratio is believed to be involved in development of hepatic encephalopathy (HE). This alteration of amino acids and their ratios is believed to be more marked with the deterioration of the liver disease itself.[4] In patients with advanced cirrhosis, HE is commonly seen in patients with cirrhosis of liver after Upper gastrointestinal bleeding. It is believed to be because of absence of isoleucine and an increased presence of leucine in hemoglobin molecules, which leads to HE by way of BCAA antagonism.[4] There is a lot of debate regarding usefulness of BCCA in HE. Multiple studies have

been conducted worldwide showing efficacy of BCCA given both by oral and IV infusion for the treatment of HE. In a recent study conducted in Peshawar it was found that clinical improvement was observed in 76.7% patients who received infusion of BCCA, as compared to 23.3% patients who received placebo.[5] The purpose of this study was to find the effectiveness of infusion of BCCA in Patients of HE. If proved to be effective, this will helpful in treatment of cirrhotic patients with HE and reduce their hospital stay.

OBJECTIVE: The objective of the study was to compare the efficacy of branched chain amino acids in reversal of hepatic encephalopathy in individuals with cirrhosis of liver when compared with placebo.

Operational Definitions:

Hepatic Encephalopathy

Hepatic encephalopathy is characterized by alteration in level of consciousness, disturbance in behavior and changes in personality, fluctuating neurological signs, flapping tremors and characteristic EEG changes (A slowing or reduced frequency of brain waves)

Grades of Hepatic Encephalopathy

Grade-I: Slight confusion, euphoria or depression, slurred type of speech, reversal of sleep pattern.

Grade-II: Moderate confusion, lethargy

Grade-III: Marked confusion, non-coherent speech, arousable on painful stimulus

Grade-IV: Deep Coma, initially responsive to noxious stimuli, later unresponsive.

BCAAs DOSAGE: Branched chain amino acids administration at a dose of 1.2g/kg/day through I/V route for 3 days.

Reversal of hepatic encephalopathy

Reversal of hepatic encephalopathy from grade-IV, grade III to grade-I after 3 days of treatment with branched chain amino acids was considered effective.

METHODOLOGY

Study Design: This Randomized control trial.

Setting: Medical Unit V, DHQ Hospital, Faisalabad.

Period: Study was carried out for a period of six months from 1st July 2016 to 30 December 2016.

Sample Size: Sample size was calculated by using WHO sample size calculator for 2 proportions P1=25%.[6] P2=56.5%.[6] Level of significance=5% Power of test=80%. Sample size was 60 patients divided in two equal groups of 30 each. Consecutive non-probability sampling technique was used.

Patients of cirrhosis of liver due to Chronic Hepatitis B,C both males and females, above 20 years of age with hepatic encephalopathy grade-IV were included in the study. Patients having renal failure, acute fulminant hepatic failure, and other metabolic causes of unconsciousness were excluded from the study.

Patients having liver cirrhosis presenting with hepatic encephalopathy grades III & IV due to liver cirrhosis because of Hepatitis B,C were diagnosed on the basis of history, clinical examination(jaundice, palmer erythema, fetor hepaticus, spider nevi, decreased liver span, ascites, splenomegaly)and relative investigations i.e LFT's, serum albumin, A/G ratio, abdominal ultrasound and PT, ascitic fluid C/E, were included in the study after excluding the other causes of unconsciousness e.g renal failure, electrolyte disturbances, sedative overdose, cerebrovascular accidents, metabolic encephalopathy and acute fulminant hepatic failure by taking history, clinical examination and investigations like RFT's, RBS,S/ Electrolytes, CT scan brain, LFT's and ABG's where needed. An informed consent from patients attendants was taken. Patients were divided into two randomly assigned equal groups by using computer generated random number table. All of the patients were given similar specific treatment i.e Lactulose 30ml 4 times a day, Bowel wash, oral Metronidazole 250mg TDS. In Study Group branched chain amino acids at dosage of 1.2g/kg/day through I/V route for 3 days were infused and compared to Control Group on placebo i.e. 5% D/W1000cc. The conscious level of patients of both groups were assessed at day0,1,2 and 3. All the data was collected and recorded on the specially designed performa.

Data was analyzed Using SPSS version 12. Quantitative variables like age were measured by Mean± Standard deviation. Frequency and percentages were calculated for qualitative variables like gender, grades of hepatic encephalopathy at day 0,1,2, and 3 and efficacy of BCCA/placebo in the groups. Chi-square test was used to compare efficacy in terms of reversal of hepatic encephalopathy in both groups. P-value less than 0.05 was taken as significant.

RESULTS

Total of 60 patients (30 in each group) were enrolled fulfilling the inclusion/exclusion criteria were included in the study.

Age distribution showed that majority of the patients were between 41-50 years in both groups, 36.67%(n=11) in Study and 43.33%(n=13) control group, 13.33%(n=4) in study and 6.67%(n=2) in control group were between 20-30 years, 26.67%(n=8) in study and 30%(n=9) in control group were between 31-40 years while 23.33%(n=7) in

study and 20%(n=6) in control group were recorded between 51-60 years of age, mean and SD was calculated as 43.56±5.21 in study group and 45.78±4.98 years in control group. (Table 1)

Table 1: Age distribution of the patients (n=60)

Age (in years)	Study group (n=30)		Control (n=30)	
20-30	4	13.33	2	6.67
31-40	8	26.67	9	30
41-50	11	36.67	13	43.33
51-60	7	23.33	6	20
Total	**30**	**100**	**30**	**100**
Mean and SD	**43.56±5.21**		**45.78±4.98**	

Gender distribution showed that 70%(n=21) patients were male in study group and 63.33%(n=19) patients in control group, 30%(n=9) patients in study group and 36.67%(n=11) in control group were females. (Table 2)

Table 2: Gender distribution of the patients (n=60)

Gender	Study group (n=30)		Control (n=30)	
Male	21	70	19	63.33
Female	9	30	11	36.67
Total	**30**	**100**	**30**	**100**

Frequency of grades of hepatic encephalopathy at day 0 was recorded in Table 3, where 93.33% (n=28) patients in study group and 100% (n=30) patients in control groups had grade-IV, 6.67% (n=2) in study group had grade-III while no patient in control group. Frequency of grades of hepatic encephalopathy at day 1 was recorded, where 53.33% (n=16) of patients in study group and 80% (n=24) of patients in control group had grade-IV HE, 30% (n=9) of patients in study group and 16.67% (n=5) of patients in control group had grade-III HE, 10% (n=3) of patients in study and 3.33% (n=1) of patients in control group had grade-II HE while 6.67% (n=2) of patients in study and no patient in control group had grade-I HE. (Table 4)

Table 3: Frequency of grades of hepatic encephalopathy at day 0 (n=60)

Day 0	Study group (n=30)		Control (n=30)	
Grade-IV	28	93.33	30	100
Grade-III	2	6.67	00	00
Grade-II	00	00	00	00
Grade-I	00	00	00	00
Total	**30**	**100**	**30**	**100**

Table 4: Frequency of grades of hepatic encephalopathy at day 1 (n=60)

Day 1	Study group (n=30)		Control (n=30)	
Grade-IV	16	53.33	24	80
Grade-III	9	30	5	16.67
Grade-II	3	10	1	3.33
Grade-I	2	6.67	00	00
Total	**30**	**100**	**30**	**100**

Frequency of grades of hepatic encephalopathy at day 2 was recorded, where 13.33%(n=4) of patients in study group and 63.33%(n=19) of patients in control group had grade-IV HE, 23.33%(n=7) of patients in study group and 23.33%(n=7) of patients in control group had grade-III HE, 36.67%(n=11) of patients in study and 10%(n=3) of patients in control group had grade-II HE while 26.67%(n=8) of patients in study and 3.33%(n=1) of patients in control group had grade-I HE. (Table No. 5)

Table 5: Frequency of grades of hepatic encephalopathy at day 2 (n=60)

Day 2	Study group (n=30)		Control (n=30)	
Grade-IV	4	13.33	19	63.33
Grade-III	7	23.33	7	23.33
Grade-II	11	36.67	3	10
Grade-I	8	26.67	1	3.33
Total	**30**	**100**	**30**	**100**

Frequency of grades of hepatic encephalopathy at day 3 was recorded, where no patient in study group and 10%(n=3) of patients in control group had grade-IV HE, 6.67%(n=2) of patients in study and 53.33%(n=16) of patients in control group had grade-III HE, 30%(n=9) of patients in study and 10%(n=3) of patients in control group had grade-II HE while 63.33%(n=19) in study and 26.67%(n=8) in control group had grade-I HE. (Table No. 6)

Table 6: Frequency of grades of hepatic encephalopathy at day 3 (n=60)

Day 3	Study group (n=30)		Control (n=30)	
Grade-IV	00	00	3	10
Grade-III	2	6.67	16	53.33
Grade-II	9	30	3	10
Grade-I	19	63.33	8	26.67
Total	**30**	**100**	**30**	**100**

Comparison of efficacy of branched chain amino acid in reversal of hepatic encephalopathy with placebo was done in Table No. 7, where 63.33%(n=19) of patients in study group and 26.67%(n=8) of patients in control group showed effectiveness in reversal of hepatic encephalopathy, while 36.67%(n=11) of patients in study and 73.77%(n=22) of patients in control group had no efficacy, p value was 0.001 i.e. ≤0.05 (Table No. 7)

Table 7: Comparison of efficacy of branched chain amino acids in reversal of hepatic encephalopathy with placebo (n=60)

Efficacy	Study group (n=30)		Control (n=30)	
Yes	19	63.33	8	26.67
No	11	36.67	22	73.77
Total	**30**	**100**	**30**	**100**

P value=0.001

DISCUSSION

Cirrhotic patients are mostly deficient in sufficient BCAAs and therefore encounter many metabolic abnormalities. Branched-chain amino acids (BCAAs) comprising leucine, isoleucine and valine act not only as substrates of proteins and as key regulators for various metabolic pathways.[7] Patients with cirrhosis of liver often have deficient BCAAs and as a result suffer from different metabolic abnormalities. In addition to urea cycle of liver, detoxification of ammonia in skeletal muscles occurs through amidation process for glutamine synthesis using BCAAs. Therefore, BCAA supplementation may increase the detoxification of ammonia in skeletal muscles and therefore can be a possible therapeutic option for treatment of HE.[7] Various studies have been conducted worldwide trying to establish efficacy of BCCA in HE. A Cochrane systematic review included 11 randomized clinical trials on the effectiveness of BCAA in patients with cirrhosis of liver when compared with control interventions. It has evaluated whether BCAA benefit patients with cirrhosis of liver suffering from HE.[8] 16 randomized clinical trials including 827 participants with hepatic encephalopathy classified as overt HE (12 trials) or minimal HE (four trials). Eight trials assessed the effectiveness of oral BCAA supplements and seven trials assessed the role of intravenous BCAA. BCAA proved to have a beneficial effect in the treatment of hepatic encephalopathy (RR 0.73, 95% CI 0.61 to 0.88;).[8] The analyses showed that BCAA had a useful role in the treatment of hepatic encephalopathy. In a study conducted in Peswahar, it was found that After the administration of BCAA infusion twice daily for 3 days, clinical improvement was observed in 33 (76.7%) patients in group taking infusion of BCCA while in group taking placebo only 10 (23.3%) patients improved clinically, showing p-value 0.001.[5] In our study, 63.33%(n=19) of patients in study group and 26.67%(n=8) of patients in control group showed effectiveness in reversal of hepatic encephalopathy.

CONCLUSION

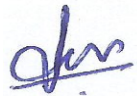
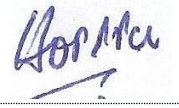
Administration of BCAAs is a promising treatment option for the treatment of patients with cirrhosis of liver having hepatic encephalopathy. The results of the study conclude that branched chain amino acids are significantly effective in reversal of hepatic encephalopathy when compared with placebo. Larger studies are needed for further confirmation of the effectiveness of BCCAs in HE due to cirrhosis of liver.

REFERENCES

1. Bleibel W, Al-Osaimi AMS, Hepatic Encephalopathy, Saudi J Gastroenterol 2012;18(5):301-9.
2. Bismuth M, Funakoshi N, Cadranel JF, Blanc P. Hepatic encephalopathy: From pathophysiology to therapeutic management. Eur J Gastroenterol Hepatol. 2011;23:8–22
3. Butterworth RF. Editorial: Rifaximin and minimal hepatic encephalopathy. Am J Gastroenterol 2011;106:317–8.

4. Tajiri K, Shimizu Y, Branched-chain amino acids in liver diseases. World J Gastroenterol 2013;19(43):7620-29.
5. Afridi MAR, Ahmad A, Ali Z, Farooqi JI, Mohammad R, Alam I. Comparative study of branched chain amino acids infusion with conventional treatment in patients with hepatic encephalopathy due to liver cirrhosis. KMUJ 2014;6(4):163-66.
6. Afzal S, Ahmad M. Role of branched chain amino acids in reversal of hepatic encephalopathy Ann King Edward Med Uni 2010;16(2):108-11.
7. Kawaguchi T, Taniguchi E, Sata M. Effects of oral branched-chain amino acids on hepatic encephalopathy and outcome in patients with liver cirrhosis. Nutr Clin Pract 2013;28(5):580-8.
8. Gluud LL, Dam G, Les I, Córdoba J, Marchesini G, Borre M et al. Branched-chain amino acids for people with hepatic encephalopathy. Cochrane Database Syst Rev 2015;25(2):CD001939.

AUTHORSHIP AND CONTRIBUTION DECLARATION

AUTHORS	Contribution to The Paper	Signatures
Dr. Umair Ahmed Assistant Professor, Medicine FMU/Allied Hospital, Faisalabad	Main researcher, Data Collection	
Prof. Dr. Aamir Shaukat Professor of Medicine FMU/Allied Hospital, Faisalabad.	Literature review	
Dr. Hooria Aamir Assistant Professor, Physiology Faisalabad Medical University, Faisalabad	Literature review	
Dr. Awais Ahmed Consultant Radiologist Shifa International, Hospital, Islamabad	Article writing, References collection