COMPARATIVE STUDY OF BRANCHED CHAIN AMINO ACIDS INFUSION WITH CONVENTIONAL TREATMENT IN PATIENTS WITH HEPATIC ENCEPHALOPATHY DUE TO LIVER CIRRHOSIS

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ABSTRACT

OBJECTIVE: To determine the effectiveness of branched chain amino acid (BCAA) infusion with conventional therapy in the treatment of hepatic encephalopathy (HE) due to liver cirrhosis.

METHODOLOGY: This was a hospital based randomized controlled trial, conducted in the department of medicine, Lady Reading Hospital, Peshawar from February 2012 to July 2012.

A total number of 86 patients, of either gender, presenting with grade II, III and IV HE due to cirrhosis were included in the study. They were randomly allocated into two groups by lottery method. Forty three patients in group A were subjected to conventional treatment plus infusion of BCAA (Aminoleban, Otsuka); while 43 patients in group B were subjected to conventional treatment only, which consisted of antibiotics and lactulose. Data analysis was performed using SPSS version 20. 'Chi square' test was used to compare the effectiveness in both groups with p value of < 0.05 as significant.

RESULTS: Out of 86 patients included in the study, 52(60.5%) were males and 34 (39.5%) were females. Mean age of the sample was 49.73±7.958 years with age range from 35 to 70 years. After the administration of BCAA infusion twice daily for 3 days, clinical improvement was observed in 33 (76.7%) patients in group A while in group B only 10 (23.3%) patients improved clinically, showing p-value <0.001.

CONCLUSION: Branched chain amino acids infusion is more effective than conventional therapy in the treatment of HE due to liver cirrhosis.

KEY WORDS: Hepatic Encephalopathy, Chronic Liver Disease, Branched Chain Amino acid, Randomized Controlled Trial.

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INTRODUCTION

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome characterized by cognitive and motor deficits of varying severity, which can develop in the course of acute and chronic decompensated liver disease.[1-5] An annual rate of 8% of HE in cirrhotic patients have been reported in the Far Eastern studies. It, therefore, remains a serious complication of liver cirrhosis[6]. Despite improved therapeutic options, the long-term survival is still low.[3,6] The widely practiced protein restriction in cirrhotic patients lacks scientific basis.[3,7] Dietary protein restriction does not have any beneficial effect for cirrhotic patients during episode of HE[7].

Treatment options for HE include use of non-absorbable disaccharides, benzodiazepine receptor antagonists, BCAA, L-ornithine, L-aspartate and Rifaximin.[4,8] Administration of BCAA to patients with chronic liver disease stimulates hepatic protein synthesis, thus significantly improving their nutritional status and resulting in a better quality of life. Appropriate protein intake and BCAA supplementation may be helpful in prevention of HE[9-13]. The BCAA causes ammonia detoxification, corrects the plasma amino acid imbalance, and reduces brain influx of aromatic amino acids.[14-16] Apart from stimulation of hepatic protein synthesis, BCAA also reduces post injury catabolism and therefore improves nutritional status[17]. The BCAA has a role in early reversal of HE in chronic liver disease[18]. The beneficial role of BCAA supplementation in patients with HE has been docu-

mented in some studies.[9-11,19,20] However, conflicting results in different trials exist; and this issue remains unclear.[17,21]

This study was designed to compare the effectiveness of BCAA plus conventional treatment and conventional treatment alone in the management of HE due to liver cirrhosis.

METHODOLOGY

This was a hospital based, randomized controlled study conducted in the Department of Medicine, Postgraduate Medical Institute, Lady Reading Hospital, Peshawar from February 2012 to July 2012. The study was conducted after approval from the Institution's Ethical and Research Committee. A total of 86 patients, of either gender, admitted to medical ward through Emergency or outpatient departments were included in the study. Two groups of 43 patients each were made, with power of study as 80% (0.80), and a large effect size of 0.6. The diagnosis of HE with liver cirrhosis was based upon 'West Haven's Criteria' and patients with grade II, III and IV were included in the study. Effectiveness of treatment was determined in terms of improvement in at least one grade of HE from baseline at 3rd day post treatment. An informed written consent was taken from the relatives of all patients.

A detailed history was taken and meticulous physical examination performed. The baseline condition of each patient was particularly graded and noted. Appropriate investigations were carried out. Venous blood was sampled from all patients and sent to hospital laboratory for Full Blood Count, Blood Sugar, Liver Functions Tests including Albumin & Prothrombin Time, Urea, Creatinine & Electrolytes, Viral serology and Abdominal Ultrasonography. All patients were randomly allocated into two groups, of 43 patients each, by lottery method. Patients in Group A (Experimental group) were subjected to conventional treatment Plus infusion of BCAA in the form of Aminoleban (Otsuka Pakistan Ltd.), 500 ml intravenous twice a day for three days; while patients in Group B (Control group) were subjected to conventional treatment only, which consisted of antibiotics, lactulose and the treatment of precipitating factor(s).

Patients in both groups were monitored closely and finally at 3rd post treatment day to determine the effectiveness in terms of improvement in at least one grade of HE from the baseline. All the above mentioned information, including bio data of the patient were recorded in a predesigned proforma.

All patients with HE Grade II, III and IV due to liver cirrhosis of age group above 30 years; of either gender were included in the study.

Patients with hepatorenal syndrome, hyponatremia, hypoglycemia and Patients with concomitant stroke were excluded from the study.

DATA ANALYSIS PROCEDURE

All the data were entered, stored and analyzed in SPSS version 20. Mean ± Standard Deviation was calculated for numerical variables like age. Frequencies and percentages were calculated for categorical variables like gender and effectiveness. Statistical analysis, using Chi square test, to compare the effectiveness in both groups while keeping p value of < 0.05 as significant. All results were presented in the form of tables.

RESULTS

Out of 86 patients included in the study, 43 each in group A and B, 52(60.5%) were male and 34(39.5%) were female, with male to female ratio of 1.5:1. In group A, 28(65.1%) patients were male and 15(34.9%) were female while in group B, 24(55.8%) were male and 19(44.2%) female.

Age of the patients ranged from 35 to 70 years with mean age of 49.73±7.958 years. Mean age in group A was 49.13±7.284 years while mean age in group B was 50.02±8.656 years, as shown in Table I.

The cause of liver cirrhosis was chronic hepatitis B in 22(25.6%), chronic hepatitis C in 43(50%) and both hepatitis B & C in 5 (5.8%) patients. In 16 (18.6%) patients, the cause was non-B, non-C hepatitis.

At the time of presentation, out of 43 patients in group A, 19(44.2%) were in grade II, 14(32.6%) in grade III and 10(23.3%) in grade IV of HE. While in group B, out of 43 patients, 16(37.2%) were in grade II, 17(39.5%) in grade III and 10(23.3%) in grade IV of HE.

After the administration of BCAA infusion twice daily for 3 days, clinical improvement was observed in 33(76.7%) patients in group A; while in group B only 10 (23.3%) patients improved clinically (p value =0.001), as shown in Table II. Sub-group analysis of improved patients in both groups (group A and group B) is shown in Table III.

DISCUSSION

Development of HE in cirrhotic patient is associated with an increased mortality. Early diagnosis and prompt management leads to better quality of life in such patients.[22] In the USA, development of HE in patient with chronic liver disease was associated with 50% one-year survival and 20% five-year survival.[23] The high concentrations of BCAA and low concentrations of aromatic amino acids is effective in decreasing GABA levels in brain, an inhibitory neurotransmitter, causing improvement in HE.[24]

To compare the effectiveness of the conventional and experimental therapy in the two groups, Chi square was applied. Success rate of BCAA (76.7%) in terms of clinical improvement in experimental Group A was significantly greater than

TABLE I: AGE WISE DISTRIBUTION OF PATIENTS IN THE TWO GROUPS (N=86)

Group	Gender	N	Minimum years	Maximum years	Mean (years)	Standard Deviation
Group A	Male	28	39	65	49.61	7.310
	Female	15	41	64	49.13	7.482
	Total	43	39	65	49.44	7.284
Group B	Male	24	36	70	52.17	8.835
	Female	19	35	62	47.32	7.825
	Total	43	35	70	50.02	8.656
Total	Male	52	36	70	50.79	8.072
	Female	34	35	64	48.12	7.615
	Total	86	35	70	49.73	7.958

TABLE II: EFFECTIVENESS OF THERAPY IN THE TWO GROUPS (N=86

Clinical Improvement	Group		P value
	Group A	Group B	0.001
Yes	33 (76.7%)	10 (23.3%)	
No	10 (23.3%)	33 (76.7%)	
Total	43	43	

TABLE III: SUB-GROUP ANALYSIS OF EFFECTIVENESS OF THERAPY IN TWO GROUPS (N=43)

Baseline Grade of Hepatic Encephalopathy	Clinical Improvement Group A	Clinical Improvement Group B	P value
Grade II	16	7	p = 0. 01
Grade III	9	2	p = 0.001
Grade IV	8	1	p = 0.001
Total	33	10	p = 0.001

conventional therapy (23.3 %) in Control Group B with p=0.001. This is in conformity with the study reported by Soomro et al from Hyderabad Pakistan, in which BCAA infusion resulted in significant improvement and early recovery from HE.[10] Afzal et al also reported 56% success rate for BCAA in his study with little difference.[18] This difference could be attributed to the differences in the sample size or the grade of HE with which patients were included in the two studies.

According to our study, BCAA has a role in early reversal of HE in chronic liver disease. After giving BCAA there was significant improvement in HE within three days (p =0.001). This is in conformity with the results of a study done in Hyderabad[10] and Faisal Abad[18] Pakistan.

In Thailand, Tangkijvanich et al, had shown similar results in their study in which BCAA had lead to improvement in hepatic metabolic capacity.[25] Suzuki K et al, had also favored use of BCAA in reversal of hepatic encephalopathy in liver cirrhosis.[26] In the United Kingdom, Metcalfe et al, in a recent systematic review found BCAA supplementation useful in cirrhotic patients with HE.[27] Studies from Denmark revealed that BCAAs have a beneficial effect on manifestations of hepatic encephalopathy in randomized controlled trials, but no effect on survival.[11] Gludd et al. from Denmark, in a meta analysis of studies showed that BCAA supplementation have beneficial effects on manifestations of HE compared with control groups.[4] In Germany, low levels of BCAA, Isoleucine documented in cirrhotic patients with HE which were successfully treated with Isoleucine infusion.[14] Similarly Bak et al, reported that BCAA, particularly isoleucine, was found beneficial in brain energy metabolism in patients of HE and its role in cancer have also been suggested.[28]

In Japan, BCAA treatment in HE patients have been evaluated extensively and found beneficial in these patients[9,15,29]. Supplementation of BCAA have been found useful in cirrhotic patients with sleep disturbance.[19] In a randomized study from Spain, BCAA supplementation resulted in improvement of HE and muscle mass in cirrhosis liver patients.[30] In Italy, Fabbri et al, concluded from the results of two largest studies that use of BCAA in the treatment of chronic HE may only be proposed for patients with advanced chronic liver disease.[31] This also favors the results of our study.

On the other hand, earlier in a Cochrane Database Review in 2003, the Cochrane Hepatobilliary Group did not find convincing evidence that BCAA had significant beneficial effect on patients with HE. The Group, however, concluded that the trials were small in size and of short follow up and low methodological quality[21].

CONCLUSION

The results of this study showed that BCAA infusion plus conventional treatment was more effective than conventional treatment alone in the treatment of patients with HE due to liver cirrhosis.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

MARA: Conceived the idea and planned the study, Acquisition of data, Drafting and writing of the manuscript, final approval of the version to be published

AA: Data collection, Statistical analysis and interpretation of data, final approval of the version to be published

ZA, JIF, RM: Acquisition of data, Drafting and revision of the manuscript, final approval of the version to be published

IA: Critical revision, final approval of the version to be published

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.