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A RANDOMIZED, OPEN LABEL, COMPARATIVE STUDY OF ORAL BRANCHED CHAIN AMINO ACIDS IN PATIENTS WITH MINIMAL HEPATIC ENCEPHALOPATHY

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ABSTRACT

OBJECTIVE: To evaluate the efficacy and tolerability of Oral branched chain amino acids in patients with minimal hepatic encephalopathy.

METHODOLOGY: The study was conducted in adult patients with *Minimal hepatic encephalopathy* attending the outpatient department of Hepatology at Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai between April 2009 –Dec2009 .Treatment period is two weeks per patients. Sample size is 40. (20 patients – study drug & standard treatment, 20 patients – standard therapy alone). The recruited patients were randomized by simple randomization into either group A or group B and received the respective therapy. (Group A: Standard therapy - Syrup lactulose 15-30 ml thrice daily for two weeks. Group B: Standard therapy with oral branched chain amino acids 3 sachets per day for two weeks).

RESULTS: 53 patients were screened out of which 42 patients were included in the study and 40 patients completed the study and were included in the analysis, two patients were lost to follow up. The patients with MHE were assessed with the psychometric tests- number connection test and line tracing test. The scores were statistically significant with clinical improvement when standard therapy is added with branched chain amino acid as compared to standard therapy alone.

CONCLUSION: In patients suffering from hepatic encephalopathy, plasma concentration of branched chain amino acids such as leucine, isoleucine and valine are decreased. Branched chain amino acids were reported to improve nitrogen metabolism, blood ammonia level, and psychomotor tests thereby improving the quality of life. BCAA supplementation along with syrup lactulose in effective in the management of minimal hepatic encephalopathy.

INTRODUCTION

Minimal hepatic encephalopathy is defined as the condition in which patients with liver cirrhosis show several quantifiable neuropsychological defects together with a normal neurological examination. [1,2,3,4]

In patients suffering from hepatic encephalopathy, plasma concentration of aromatic amino acids such as phenylalanine, tyrosine and free tryptophan as well as methionine, aspartic acid and glutamine are elevated whereas branched chain amino acids such as leucine, isoleucine and valine are decreased [5,6,7].

Lactulose is considered the gold standard of the treatment of minimal hepatic encephalopathy. The efficacy of lactulose is due to an interaction with the intestinal flora and decrease in the generation of nitrogenous compounds in the intestine[7].

Branched chain amino acid has a peculiar role in whole-body nitrogen metabolism. Branched chain amino acids are a substrate for protein synthesis, and have been used to conserve or restore muscle mass in advanced liver disease. In addition, the competitive action of branched chain amino acid on amino acid transport across the blood-brain barrier may improve hepatic encephalopathy[8,9,10].BCAA supplementation not only improves hypoalbuminemia, but also reduces the occurrence and frequency of various complications of liver cirrhosis, which considerably affect mortality[11,12].

2.0 METHODOLOGY

2.1 OBJECTIVE:

This randomized, open label, study was done to assess the efficacy and tolerability of Oral branched chain amino acids 3 sachets per day for two weeks along with syrup lactulose15-30 ml thrice daily for two weeks in patients' with minimal hepatic encephalopathy in comparison to standard therapy (Syrup lactulose 15-30 ml thrice daily for two weeks).

2.2 STUDY DESIGN

This was a randomized, open label, comparative study done at Department of Hepatology, Rajiv Gandhi Government General Hospital , Madras Medical college, Chennai. The study was carried out from April 2009 –Dec2009 for 2 weeks per patient. Adult patients with minimal hepatic encephalopathy were the study population .Total number of patients was 40, two groups with 20 patients in each group. (Control & study group)

2.3 SELECTION CRITERIA

2.3.1 INCLUSION CRITERIA:

- Age – 20-50 yrs
- Sex –both genders
- Cirrhosis of liver with minimal hepatic encephalopathy
- Patient willing to give written informed consent

2.3.2 EXCLUSION CRITERIA

- H/o hepatic encephalopathy grade 1,2,3,4.
- Acute hepatic encephalopathy.
- Hepatic encephalopathy due to metabolic causes, intracranial disorders and toxins.
- Subject undergone treatment with amino acid and albumin infusion [oral and parentral] within the past 6 weeks

2.4 STUDY PROCEDURE

The study protocol was submitted to the Institutional Ethical Committee and approval was obtained. **(No .006859).** Written informed consent was obtained from patients who were willing to participate in the study, in the prescribed format in regional language prior to the performance of any study related procedures.42 patients were screened and 20 patients in each group were randomized into either group A (control group) or group B (study group)

2.5 TREATMENT PLAN

20 patients in the control group received standard therapy (Syrup lactulose 15-30 ml thrice daily for two weeks).20 patients in the control group received Oral branched chain amino acids 3 sachets per day along with syrup lactulose15-30 ml thrice daily for two weeks. Patients were asked to return the empty packets during subsequent visits. Each 10 gm sachet contains L-valine USP1144 mg, L-Isoleucine USP 952 mg, L-Leucine USP 1904 mg. The sachet should be mixed thoroughly in 200 ml of potable water and consumed after each meal.

2.6 EVALUATION

Data were analyzed using SPSS 16. The age and sex distribution were analyzed by Chi square test. The laboratory parameters were analyzed by ANOVA F test and student t test. The line tracing and number connection test is analyzed by repeated measures of ANOVA. P value <0.05 was considered significant.

3.0 RESULTS

TABLE 1: LINE TRACING TEST

Study Groups	BASE LINE		DAY 8		DAY 15		Repeated Measures of ANOVA
	Mean	SD	Mean	SD	Mean	SD	
Group A	138.65	6.89	128.70	6.67	113.10	8.17	Between groups P=0.01 Within group P=0.05
Group B	135.15	11.07	120.7	8.47	100.95	7.59	

LINE TRACING TEST

FIGURE : 1

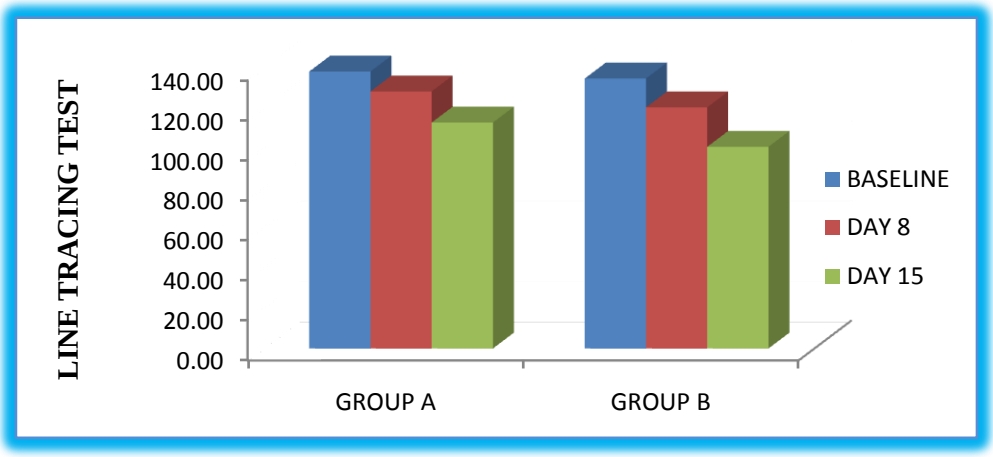

TABLE 2: NUMBER CONNECTION TEST

STUDY GROUP	BASELINE		DAY 8		DAY 15		Repeated Measures of ANOVA
	Mean	SD	Mean	SD	Mean	SD	
Group A	40.30	5.30	33.45	4.16	28.25	2.43	Between groups P=0.01
Group B	39.3	4.07	30.95	3.44	24.80	2.02	Within group P=0.05

FIGURE 2: NUMBER CONNECTION TEST

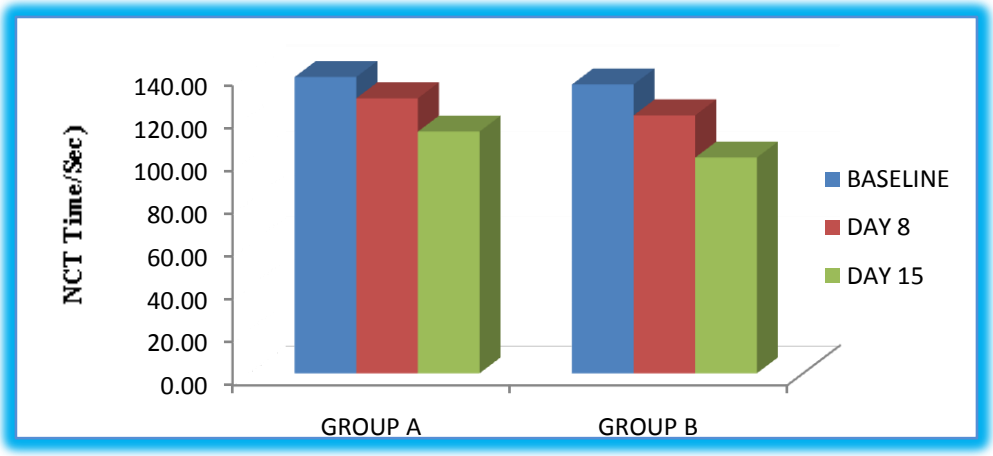

TABLE 3: SERUM PROTEIN

Study Groups	BASE LINE		DAY 15		Student paired t-test
	Mean	SD	Mean	SD	
Group A	4.94	0.29	5.57	0.35	P=0.21
Group B	5.09	0.31	6.31	0.20	P=0.03
ANOVA	P=0.12		P=0.001		

FIGURE 3 : SERUM PROTEIN

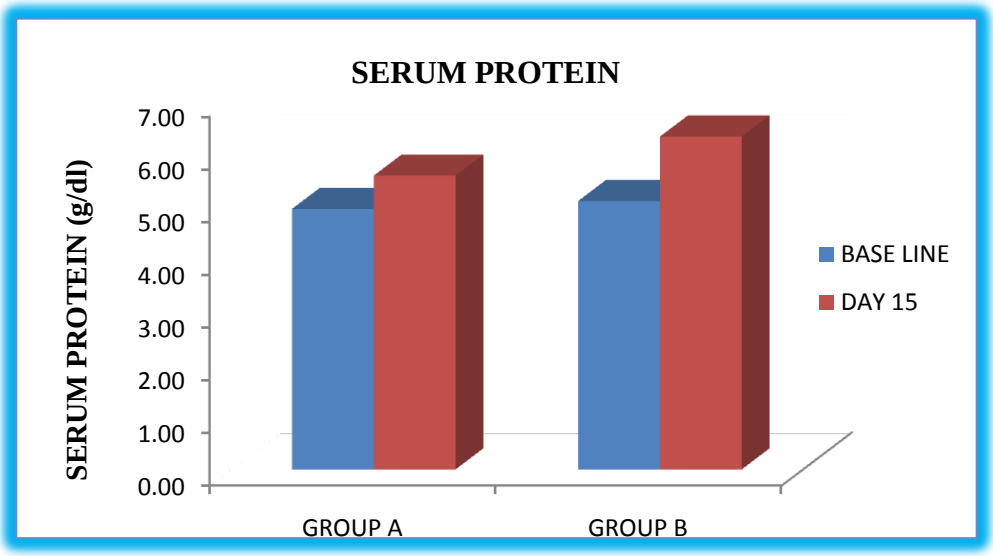

TABLE 4: AMMONIA

Study Groups	BASE LINE		DAY 15		Student paired t-test
	Mean	SD	Mean	SD	
Group A	48.45	0.51	40.40	2.16	P=0.09
Group B	48.50	0.69	38.15	2.50	P=0.27
ANOVA	P=0.796		P=0.004		

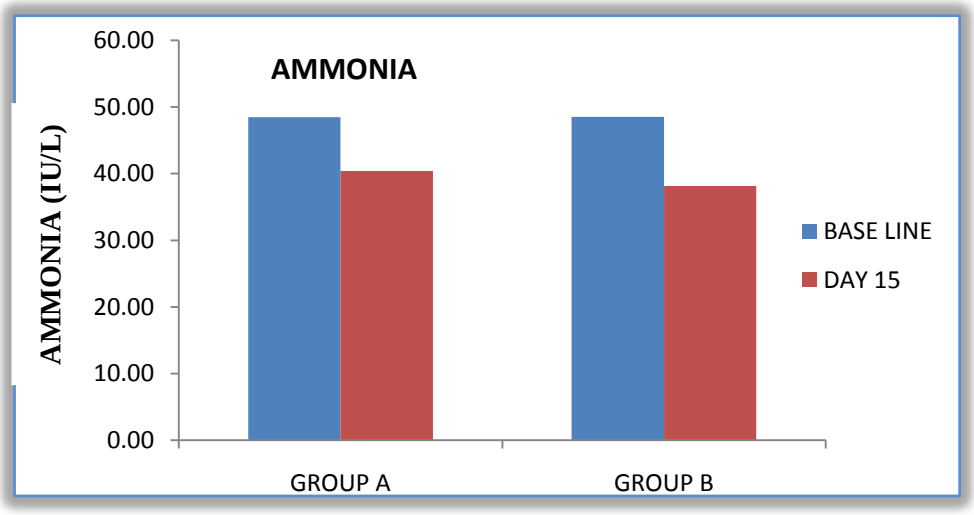

FIGURE 4

4.0 DISCUSSION

Minimal hepatic encephalopathy is a neurocognitive dysfunction that is present in majority of patients with cirrhosis of liver. Branched chain amino acids were reported to improve nitrogen metabolism, blood ammonia level, and psychomotor tests. [13,14,15,16] BCAA has a potentially therapeutic role in improving hepatic encephalopathy. [17,18,19] The therapeutic efficacy of oral branch chain amino acids with standard drug syrup lactulose in the treatment of minimal hepatic encephalopathy was assessed in this study. In our study, ammonia, which

plays an important role in minimal hepatic encephalopathy lowered and showed a statistically significant reduction [p=0.004] at the end of two week therapy. Total proteins concentration increased significantly in the BCCA group as compared with the group on standard therapy at the end of two weeks. [p=0.03]. By comparing oral BCAA with syrup lactulose improved responses were obtained on assessment with psychometric tests. [NCT p=0.01][LTT p=0.01].These findings were consistent with other studies [20,21,22] During the entire period of the study no adverse effects were observed thereby showing that branched chain amino acids were well tolerated.

5.0 CONCLUSION

In this study it has been proved that Oral branched chain amino acid is effective in minimal hepatic encephalopathy. Oral branched chain amino acid is well tolerated. No adverse effects were observed in patients who received oral BCAA.

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