Role of Branched Chain Amino Acids in Reversal of Hepatic Encephalopathy

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Objective: The objective of this study was to determine the effect of branched chain amino acids on reversal of hepatic encephalopathy. The reversal of hepatic encephalopathy was determined by time required for improvement in grade of encephalopathy and total duration of hospital stay.

Study Design: Single blinded Randomized Control Clinical Trial.

Setting and Duration: In the Gastroenterology Unit, Medical-1 Allied Hospital Faisalabad. Duration of the study was one year, started in May 2005.

Patients and Methods: Hundred cases of hepatic encephalopathy grade IV were divided in two groups of fifty each. It was random allocation of two group. After taking informed consent, group I and II, both were given standard treatment and group II received branched chain amino acids.

Results: Complete record of all the patients was maintained on the proforma and kept confidential. Six patients in group I and four patients in group II died during the study duration. 11 subjects in group 1 as compared to 26 in group II showed improvement in maximum duration of less than 3 days. ($p < 0.05$). 25 cases in group I and 9 in group II showed significant improvement in nine or more days. ($p < 0.05$). On comparison of duration of hospital stay 19 cases in group I as compared to 37 in group II showed hospital stay less than nine days ($p < 0.05$).

Conclusions: There is a role of branched chain amino acids in early reversal of hepatic encephalopathy due to chronic liver disease. However further Randomized Clinical Trials are required.

Keywords: *Cirrhosis, encephalopathy, hepatic*.

Introduction

Liver disease is common worldwide; in United Kingdom 5000 deaths from cirrhosis have occurred in a year.[1] In United States chronic liver disease is the 7th leading cause of death, according to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).[2] In Pakistan, the life of large number of population is at stake due to the large impact of hepatitis B and C viral infections and an increase in intake of alcohol that has occurred over the last decade.[3] The most dreadful complication of chronic liver disease is hepatic encephalopathy.[4] The spectrum of hepatic encephalopathy ranges from minimal cerebral functional deficits, which can only be found by sensitive psychometric tests, to coma with signs of decerebration.[5] Hepatic encephalopathy has arbitrarily been divided into stages. A number of precipitating factors are known and the first line of therapy should always be the elimination of these factors.[6] The differential diagnosis includes all states of impaired consciousness and deficits in cerebral function in patients with chronic liver disease, and clinical and biochemical tests to differentiate are indicated.

Hepatic encephalopathy is characterized by disturbances in consciousness and behaviour, personality changes, fluctuating neurological signs, asterixis and distinctive EEG changes.[7]

Patient passes through progressive stages of encephalopathy resulting in increased hospital admissions, more consumption of health care resources and above all the longer-hospital stays contribute to increase in off work hours and loss of man power resources. The therapeutic options for hepatic encephalopathy include protein restriction, antibiotics (aminoglycosides), lactulose, branched chain amino-acids.[8] The rationale for the use of branched chain amino acids in hepatic encephalopathy is the disturbance of Fischer ratio.[9] This is a molar ratio of branched chain amino acids and aromatic amino acids and disturbance causes encephalopathy. Branched chain amino acids include valine, isoleucine and leucine. The decrease in these amino acids leads to the disturbances in transport of amino acids across the blood-brain barrier which results in increased synthesis of false neurotransmitters in the brain e.g. octopamine.

The change in the permeability of blood brain barrier is an important factor in the pathogenesis of hepatic encephalopathy.[10]

Several observations suggest that increased CNS GABA is also contributory to encephalopathy because GABA is an inhibitory neurotransmitter, causing reduced levels of consciousness.

GABA concentrations in CNS are increased in hepatic encephalopathy. There was an evidence to suggest that endogenous benzodiazepines, which act through the GABA receptors, may contribute to the development of hepatic encephalopathy. This evidence included isolation of 1,4 benzodiazipines from the brain tissues of the patient.[11] Another evidence came from the study in which administration

of flumazenil, a benzodiazepine antagonist causes a good response in improving encephalopathy.[12]

The objective of the study was to determine the effects of branched chain amino acids in reversal of hepatic encephalopathy by measuring the time required for the reversibility of hepatic encephalopathy from grade 4. i.e. unresponsive coma to grade 1 .i.e., slurred speech and sleep disturbance, as determined by serial clinical examinations. Total duration of hospital stay from day of admission, in cases of hepatic encephalopathy was also measured to see the early reversal of hepatic encephalopathy.

Material and Method

This Single blinded Randomized Control Trial was carried out in one year starting from May 2005, in Gastroenterology Unit, Medical-1, Allied Hospital Faisalabad. Hundred cases were selected and divided in two groups. The sample size was calculated using Epi-info2000. It was a probability sampling with random allocation of two groups using random table. The included cases, 20-60 years of age, suffering from grade 4 encephalopathy that is unresponsive coma due to chronic liver disease on clinical examination. Clinical features of chronic liver disease found were jaundice, palmar erythema, fetor hepaticus, spider naevi, reduced liver span, and splenomegaly. The other treatable causes of unconciousness were excluded from the study e.g. Renal failure due to any cause including hepatorenal syndrome, hypertension, diabetes, hypoglycaemia, electrolyte disturbances, alcohol intoxication, sedative overdose, acute fulminant hepatic failure. Ethical issues were considered. Informed consent was taken. Risks and benefits were explained. All the information about the patient was kept confidential. All patients were given standard treatment i.e., Lactulose 30 ml till stools were passed then 30 ml 4 times a day. Metronidazole 250 mg TDS. No oral proteins were allowed. Group II was given branched chain amino acids through I/V route for 9 days, dose 1.2g/kg/day.

Both groups were assessed daily. The outcome of hepatic encephalopathy was measured in days required for the shifting of the patient from grade 4 hepatic encephalopathy to grade 1.

The total duration of hospital stay in days from the day of admission was also measured by the researcher. The end point of the study was defined as shifting of the patient to grade 1 encephalopathy from grade 4.

According to severity the stages of encephalopathy are graded as:[13]

Grade 1: sleep disorder / slurred speech.
Grade 2: flaps present / oriented.
Grade3: irritable / drowsy.
Grade4: unresponsive coma.

Proforma was used as data collection tool.

The data was analyzed using SPSS version 13.0 for windows. Table was used to present the data. Quantitative variables were presented in percentages. For comparison of proportions chi-square test was applied and p value equal or less than 0.05 was considered as significant.

Results

A total of hundred patients of hepatic encephalopathy grade IV were divided in two groups of fifty each. In group I patients received standard treatment while patient in group II were infused with branched chain amino acid in addition to standard treatment. Six patients died during the study duration in group l and four in group II. In group I, eleven patients out of forty-four of grade IV encephalopathy showed improvement to grade I in less than 3 days (25% of patients in group1). Eight patients showed improvement in 3-9 days (8.8%). Twenty-five patients showed improvement in more than 9 days (56.8%). Table 1.

In group II twenty-six patients of grade IV encephalopathy showed reversal to grade I in less than 3 days (56.5%). Eleven patients showed improvement to grade I in 3-9 days (23.9%). Nine patients showed improvement in hepatic encephalopathy in more than nine days (19.56%). Table I.

Comparison of group I and II for duration of reversal of hepatic encephalopathy had shown significant improvement in patients of group II in duration of less than three days (p=0.0012).

No statistically significant improvement was found in both groups in 3 – 9 days. (p= 0.2527). More patients in group – I had shown improvement in grades of hepatic encephalopathy in more than nine days (p = 0.0001). Thus more duration of treatment was required in group I for reversal of hepatic encephalopathy as compared to group – II. Statistically significant difference was found. (p<0.05).

The comparison of total duration of hospital stay showed that the patients in group II had statistically significant difference in lesser hospital stay than cases in group I. (p=0.0001).

Thirty seven patients in group II, as compared to nineteen patients in group I had

Table 1: *Comparison of duration of reversal of encephalopathy from Grade-IV to Grade-I in Two groups.*

Sr. No.	Duration in days	Group-1	Group-II	P-value
1.	< 3 days	11	26	P = 0.0012
2.	3 – 9 days	08	11	P = 0.2527
3.	> 9 days	25	09	P = 0.0001

Table 2: *Comparison of duration of Hospital stay in two groups.*

Sr. No.	Duration in days	Cases in Group-1	Cases in Group-II	P-value
1.	< 9 days	19	37	P = 0.0001
2.	> 9 days	25	09	P = 0.0001

hospital stay less than nine days. (p=0:0001).

Nine patients in group II had hospital stay equal or greater than nine days, as compared to twenty-five in group I. (p=0.0001) Table II.

Discussion

The alarming state of deterioration of a patient having hepatic encephalopathy due to chronic liver disease, from sleep disturbance to unresponsive coma, always attract the inquisitive minds of medical researchers and physicians and the better solution of the problem has been the common objective of all research.

Chronic liver disease is the seventh leading cause of death in United States. In our country, medical wards are overburdened with the patients of chronic liver disease who are fighting hard to get rid of their miserable state. There are many precipitating factors that causes hepatic encephalopathy in chronic liver disease and diagnosis and prompt management leads to better quality of life in cirrhotic patients.[14]

In an international study, it was documented that hepatic encephalopathy developed in a patient with chronic liver disease caused decompensated cirrhosis with one-year survival 50% and five-year survival 20%.[15]

In our study the cases of hepatic encephalopathy due to chronic liver disease are given Branched chain amino acids which include valine, isoleucine and leucine. The high concentrations of branched chain amino acids (e.g. leucinc, isoleucine and valine) and low concentrations of aromatic amino acids (phenylalanine, tryptophan, tyrosine, methioninc) is effective in decreasing GABA levels in brain that is a inhibitory neurotransmitter, causing improvement in hepatic encephalopathy.[11]

According to our study, branched chain amino acids (BCAA) had a role in early reversal of hepatic encephalopathy in chronic liver disease. The total duration for reversal of hepatic encephalopathy after giving branched chain amino acids had shown that there was improvement in patients of group II with in three days (< 72 hours) (p = 0.0012). Tangkijvanich P et al had shown similar results in their study that the branched chain amino acids had lead to reversal of hepatic encephalopathy in mean duration of 56.8 hours.[16]

In this study more patients in group – I had shown improvement in grades of hepatic encephalopathy in more than nine days (p=0.0001). Thus more duration of treatment was required in group I for reversal of hepatic encephalopathy as compared to group II. Statistically significant difference was found. P=0.0009. Suzuki K et al, had shown similar results in their study on role of branched chain amino acids in reversal of hepatic encephalopathy in chronic liver disease.[17]

In a study, the effects of selected branched-chain amino acid (BCAA) enriched parenteral solutions in reversal of hepatic encephalopathy due to liver cirrhosis was considered. Groups A and B were infused for 9 days with branched chain amino acids valine, leucine; isoleucine at doses of 0.5 and 1.0 g/kg/day, respectively. Group C received 0.8 g/kg of essential and nonessential amino acid solution with a prevalence of branched chain amino acids; the last group (D) continued the basic standard treatment, as control. Branched chain amino acids led to an impressive and significant improvement in hepatic encephalopathy in both the A and B groups in less duration. The same results were obtained in group C but in longer duration. The ratio of branched chain amino acid to aromatic amino acids in groups A, B, and C was significantly increased (p less than 0.01, less than 0.02, less than 0.025, respectively). In group D the amino acid pattern and the branched chain amino acid/aromatic amino acid ratio remained unchanged.[18] In our study same results in the favor of branched chain amino acids were found i.e., statistically significant improvement was found in group II in lesser duration. P=0.0009.

In several studies, branched chain amino acids were found to decrease the duration of hospital stay.[19] Similar results were found in our study. When duration of hospital stay in group I and group II was compared, it was found that thirty-eight patients in group II had hospital stay less than nine days.($p<0.05$).

Thus branched chain amino acids decreased the unwanted socio economical load on the health care resources by decreasing the duration of stay in the hospital and by decreasing the prolonged sufferings of the patients. Rebecca Dersmonian, et al had shown the beneficial effect of branched chain amino acids on the early reversal of hepatic encephalopathy in chronic liver disease, by an aggregate relative risk reduction of 0.59 that was calculated with 95% confidence intervals of 0.23 to 0.80 ($p < 0.002$).[20]

Andrea Fabbri et al concluded that the results of the two largest, long-term studies, the use of branched-chain amino acids in the treatment of chronic encephalopathy may only be proposed for patients with advanced chronic liver disease.[21] That also favors the results of our study because the patients of hepatic encephalopathy with chronic liver disease were selected for the study and were administered BCAA. In our population many patients were never diagnosed to have liver disease till they end up in decompensated Cirrhosis and then the treatment of the complications is the focus.[22]

Due to the fact that there was short duration of follow-up in the study, it is recommended that additional RCTs with prolonged follow-up should be performed by researchers.

Conclusions

This study has shown that Branched chain amino acids have a very promising role in early reversal of hepatic encephalopathy and reduces the duration of hospital stay thus decreases the unnecessary burden on health care resources. However on the role of branched chain amino acids in reversal of hepatic encephalopathy in chronic liver disease and its effect on mortality, further studies are required.

References

1. Blei AT, Dagher L, Terg R. Hepatic enccphalopathy. Gastroenterol 2001; 96: 1968-74.
2. James JH. Branched chain amino acid in Hepatic encephalopathy. Am Surg 2002; 183: 424-29.
3. Macheisine G,Westphal J, Saito M. Nutritional treatment with branched chain amino acids in advanced liver cirrhosis. Gastroenterol 2001; 35: 7-12.
4. Hamid S, Umar M, Alam A, Siddiqui A, Qureshi H, Butt J, et al. PSG.Consensus statement on the management of hepatitis C virus infection-2003. J Pak Med Assoc 2004; 54: 146-50.
5. Gitlin N. Hapatic encephalopathy. In: Zakim I, Bayer T I (editors). Hepatology: A text book of liver diseases. 3rd ed. Philadelphia: W.B. Saunders, 1996: 605-177.
6. Geber T, Friedman I.S, Ilerman P, Iladvie S. Hepatic encephalopathy in liver cirrhosis: Pathogenesis, diagnosis, and management. Drug 2000; 60: 1353-56.
7. Mehboob F. Prognosis in decompensated cirrhosis — A complete follow-up study of twenty five cases. Ann King Edward Med Coll. 2003; 9 (3): 214-5.
8. Abbas Z, Jafri W, Shah SHA, Khokhar N, Zuberi SJ. Members of the consensus panel. PSG consensus statement on management of hepatitis B virus infection - 2003. J Pak Med Assoc 2004; 54: 150.
9. Nijveldt Wiezer MJ, Meijer C. Major liver resection results in a changed plasma amino acid pattern as reflected by decreased Fischer ratio. Liver 2001; 21: 56-63.
10. Albert Parés, Ramón Deulofeu, Laura Cisneros Angels Escorsell, Joan Manuel Salmerón, Joan Caballeríaand Antoni Mas Albumin dialysis improves hepatic encephalopathy and decreases circulating phenolic aromatic amino acids in patients with alcoholic hepatitis and severe liver failure. Critical care 2009; 13 (1): 34-8.
11. Lewling H, Breit Kreutz R, Reline F. Hyperammonia induced depletion of glutamate and branched chain aminoacids in muscle and plasma. J Hepatol 1996; 25: 756.
12. Schmidt LE, Tofteng F, Strauss GI, Larsen FS: Effect of treatment with the Molecular Adsorbents Recirculating System on arterial amino acid levels and cerebral amino acid metabolism in patients with hepatic encephalopathy. Scand J Gastroenterol 2004; 39: 974-980.
13. Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. J Viral Hepatol 2004; 11: 97-107.
14. Atiq M, Gill ML. Quality of life assessment in Pakistani Patients with Chronic Liver Disease. J Pak Med Assoc. 2004; 54 (3): 113-5.
15. Georg M. Lauer, Bruce D. Walker I. Hepatitis C Virus infection. N Engl J Med, Vol. 345, No. 1 July 5, 2001.
16. Tangkijvanich P, Mahachai V, Wittayalertpanya S, Ariyawongsopon V Sachapan I. Short term effects of branched chain amino acids on liver fuction tests in cirrhotic patients. Southeast Asian J Trop Med Public Health 2006; 31 (1): 152-57.
17. Suzuki K, Kato A,Iwai M. Branched chain amino acid treatment in the patients with liver cirrhosis. Hepatology Research 2009; 30: 25-9.
18. Shawcross D, Jalan R: Dispelling myths in the treatment of hepatic encephalopathy. Lancet 2005; 365: 431-433.
19. Khan IM, Hameed K, Abmad S, Khan A, Akbar F. Effects of aminolaban on consciousness level of liver disease. Postgrad Med Inst 2003; 17 (2): 163-7.
20. Dersimonian R. Parenteral nutrition with branched-chain amino acids in hepatic encephalopathy: Meta analysis. Hepatology 2005; 6 (2): 64-9.
21. Andrea Fabbri, Nicola Magrini, Bianchi G, Marchesini G. Overview of Randomized Clinical Trials of Oral Branched-Chain Amino Acid Treatment in Chronic Hepatic Encephalopathy. Journal of Parenteral and Enteral Nutrition 2006; 20 (2): 159-164.
22. Zakiullah M. Beware of hepatitis C, the Silent Epidemic. Med Today 2005; 3 (1): 26-34.