The Effect of L-ornithine L–aspartate and Branch Chain Amino Acids on Encephalopathy and Nutritional Status in Liver Cirrhosis with Malnutrition

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ABSTRACT

Aim: *to determine the effect of L-ornithine-L-aspartate (LOLA) together with the nutritional improvement and branched chain amino acids (BCAAs) substitution, on encephalopathy in liver cirrhosis with malnutrition.*

Methods: *liver cirrhosis patients visited Cipto mangunkusumo Hospital in June-October 2009 were evaluated by critical flicker frequency (CFF) test. Encephalopathy is defined when CFF <39Hz. Nutritional status is measured by the mid-arm muscle circumference (MAMC) and is stated as malnutrition when MAMC <15%. All subjects who fulfilled the inclusion criteria received education for adequate calories and protein intake, and then they were be divided into 2 groups by randomization. One group was given LOLA granules 3 x 6 g/d for 2 weeks, while another group was not. Then their prealbumin and CFF test were measured again. Statistical analysis conducted for this double blind randomized clinical trial was independent student t test.*

Results: *there were 34 liver cirrhosis patients fit the inclusion criteria, and by randomization 17 subjects were put into group A (received LOLA) and 17 subjects into group B (without LOLA). Statistical analysis obtained the statistically significant (p=0,016) of increasing of the mean CFF value in group A (2.41±1.6 Hz) compared to group B (0.67±2.3 Hz). However, there was not significant increasing of prealbumin level in group A compared to group B (1±1.3 mg/dL vs 1.2±1.4 mg/dL, respectively (p=0,59). Furthermore, after 2 weeks of treatment there was no significant increase of ureum and creatinine level in both groups (4±0.5 mg/dL vs 9.3 ±1.3 mg/dL, (p=0.4) for ureum, -0.1 (0.1) mg/dL vs 0.1±0.1 mg/dL, (p=0.3) for creatinine.*

Conclusion: *minimal hepatic encephalopathy with malnutrition can be given a diet of 35-40 cal/kgBW and 1.5 g protein/kgBW including BCAA substitution to improve nutritional status, and LOLA granules can be given to improve encephalopathy.*

Key words: *minimal hepatic encephalopathy, malnutrition, CFF, LOLA, prealbumin, BCAAs.*

INTRODUCTION

Hepatic encephalopathy (HE) is one of the complications in liver cirrhosis with high morbidity and mortality.[1-4] Minimal hepatic encephalopathy (MHE) is clinically asymptomatic but there is impairment in the psychometric test. MHE has been found to affect the quality of life[5-10] and is the risk of development of overt HE.[11,12]

In recent years, critical flicker frequency (CFF) test has been developed for the diagnosis of MHE. It is easier and less influenced by educational level of patients compared to psychometric test.[12-14] Based on the hypothesis that retinal gliopathy could serve as a marker of cerebral gliopathy in HE, we investigated whether assessment of visual function by determining the CFF is suitable for diagnosis and quantification of low-grade HE.[15-17]

Increased ammonia in HE resulted in increase of peripheral benzodiazepines receptor (PBR), subsequently reactive oxygen species (ROS) which is also increased, followed by mitochondrial dysfunction, resulting in abnormalities in the brain astrocyte which then can lead to HE.[18] Therefore, the management of HE is intended to lower ammonia levels, including by limiting protein intake. However, this restriction would lead to malnutrition.[19]

Malnutrition incidence in liver cirrhosis ranges between 65-90%. This is partly the result of poor nutritional intake caused by encephalopathy and protein restriction.[19] On the other hand, liver cirrhosis with malnutrition has a higher incidence of encephalopathy.[19-20]

Today, L-ornithine-L-aspartate (LOLA) has begun to be used to treat HE since it was proven to reduce ammonia level.[21-24] LOLA stimulates the urea cycle and glutamine synthesis, which is an important mechanism in the detoxification of ammonia.[25] With LOLA, there is no need to restrict the protein intake any longer. ESPEN 1997 and 2006 recommended 35-40 kcal /kg/ day and 1.5 g protein/kg/day for liver cirrhosis with malnutrition.[26] ESPEN also recommended the use of branch chain amino acids (BCAA) to improve the nutritional status of liver cirrhosis with malnutrition.[26-29] Based on the above issues, it is necessary to do a research to prove that the nutritional status in liver cirrhosis patient with MHE and malnutrition can be improved with adequate protein intake without exacerbating the MHE. It is also necessary to examine whether a diet of 35-40 kcal/kg/day and 1.5 g protein/kg/day with BCAA substitution along with LOLA would improve both HE and malnutrition.

The aim of this study is to evaluate the influence of LOLA together with the nutritional improvement and BCAA substitution, to encephalopathy in liver cirrhosis with malnutrition.

METHODS

This double blind clinical trial was conducted at Cipto Mangunkusumo and Koja Hospitals between June 2009 and October 2009. The diagnosis of liver cirrhosis was established histologically or based on the presence of at least two of the following: characteristic imaging features, oesophageal or gastric varices, ascites or increased international normalized ratio (INR) that could not be attributed to any other cause.[20]

MHE is measured with *HEPAtonorm™Analyzer*, CFF <39 Hz was considered to have encephalopathy.[6,7] Nutritional status was assessed by mid-arm muscle circumference (MAMC). Patients were considered to be malnourished when MAMC was below the 15th percentile, according to Frisancho reference data (NHANES I and II).[30-32]

Prealbumin was taken to assess the nutritional status improvement,[33,34] performed with nephelometric technique. Adequate calorie and protein intake with BCAA substitution means 35-40kcal/kgBW and protein 1,2-1,5 g/kgBW[19,26] including BCAAs (*hepatosol*â) 2 x 60 grams, to reach the improvement of nutritional status. Urea and creatinine levels before and after the interventions were measured to evaluate the side effects to renal function.[35]

Inclusion criteria were liver cirrhosis with MHE (CFF test <39Hz) and malnutrition (MAMC below the 15th percentile). Subjects were excluded if there was an acute infection, gastrointestinal bleeding, creatinine level above 3 mg/dl, concentration disturbances and visual impairment. All liver cirrhosis patients who meet the inclusion criteria were tested for their MAMC and CFF. Blood was taken for the examination of prealbumin, albumin, bilirubin, prothrombin time, urea, creatinine and ammonia. Education was given for adequate calories and protein intake. One group was given LOLA granules (*Hepamerz*) 3 x 6 g/d for 2 weeks, while another group was not. Then their prealbumin and CFF test were measured again.The calculation of sample size obtained 34 people, and with randomization they were divided into 2 groups, which were 17 subjects for group A and 17 subjects for group B.

Statistical analysis conducted for this trial was independent student t test. This research has received ethical clearance from the Committee of the Medical Research Ethics of the Faculty of Medicine, University of Indonesia.

RESULTS

From June 2009 to October 2009, 34 liver cirrhosis patients who fulfilled the inclusion criteria were obtained. After randomization, 17 people were put into group A (received LOLA) and the other into group B (without LOLA). No patients experienced constipation during the intervention and also, no patients fell into an overt HE. Of all patients who completed the study, no one complained about the side effects of the consumed BCAA or LOLA. (**Table 1**)

Thirty one men and 3 women were obtained. The mean age is 52.5±10.9 years, with a range between 23-72 years old. The proportion of 40-60 year age group is the highest among the study subjects (71%), whereas 20% are those above 60 years and only 9% under 40 years of age. Most have a Child Pugh score B (91.2%), as could be seen in **Table 1**.

Results of The CFF Test in Nutritional Improvement Including BCAA Substitution in Group with LOLA Compared to Group without LOLA

Statistical analysis using unpaired t test, obtained that the mean increasing of the CFF value in the group

Table 1. Characteristics of 34 study subjects

Variables	Total patients	Groups		p
		A	B	
Number of (%) Subjects	34	17 (50%)	17 (50%)	
Gender				
- Male	31 (91,2%)	16 (94,1%)	15 (88,2%)	0,5
- Female	3 (8,8%)	1 (5,9%)	2 (11,8%)	
Age (Years)	52,5 ± 10,9	53,2 ± 11,8	51,8 ± 10,6	0.8
Child Pugh				
- B	31 (91,2%)	15 (88,2%)	16 (94,1%)	0,5
- C	3 (8,8%)	2 (11,8%)	1 (5,9%)	
Ammonia level (μmol/L)	140,9±36	146,9±38	134,9±33,8	0,3
Ureum level (mg/dL)	25,6±8,5	22.8±8,4	29,3±7,8	0,1
Creatinin level (mg/dL)	0,8±0,1	0,8±0,1	0,8±0,2	0,6

A was 2.41±1.6 Hz, while in the group B was of 0.67±2.3 Hz, and this difference was statistically significant (p=0,016) as shown in **Table 2** and **Figure 1**.

Table 2. The mean increase of CFF test with LOLA and without LOLA

Variables	Before (mean±sd)	After (mean±sd)	Different (mean±sd)	p
CFF in group A	34,1±2,5	36,5±2,9	2,4±1,6	<0,001
CFF in group B	35,6±2,1	36,3±2,8	0,7±0,7	0,246
Mean increase [delta CFF (Hz)]			p=0,016	

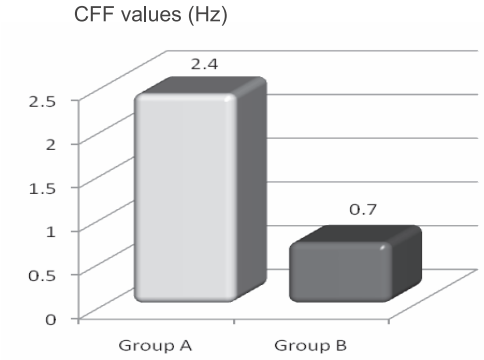

Figure 1. The mean increase of CFF values in both groups

Prealbumin in Nutritional Improvement Including BCAA Substitution in Group with LOLA Compared to The Group without LOLA

Statistical analysis using unpaired t test, obtained that in general the increasing level of prealbumin in the group A was 1±1.3 mg/dL, compared with 1.2±1.4 mg/dL in group B, and this difference was not statistically significant (p=0,59) as shown in **Table 3** and **Figure 2**.

Table 3. The mean increase of prealbumin level with LOLA and without LOLA

Variables	Before (mean±sd)	After (mean±sd)	Different (mean±sd)	*p*
Prealbumin (A)	5.4±2.1	6.4±2.6	1±1.3	0,008
Prealbumin (B)	6,5±3,7	7,7±4,4	1.2±1.4	0,003
Mean increase [delta Prealbumin (mg/dL)]			P=0,59	

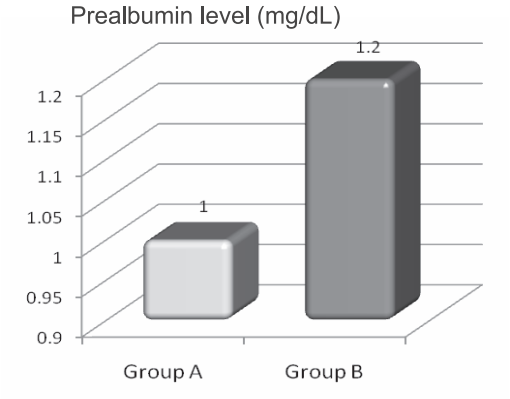

Figure 2. The mean increase of prealbumin level in both groups

In general the mean increase of ureum after intervention in group A was 4±0.5 mg/dL and in group B was 9.3±1.3 mg/dL. Mean difference of increasing in the both groups was not statistically significant (p=0.4). The increase of creatinine after intervention in group A was -0.1 (0.1) mg/dL compared with 0.1±0.1 mg/dL in group B. The increase of mean difference in both groups was also not statistically significant (p=0.3).

DISCUSSION

Kircheis (1997) conducted a clinical trial of LOLA that was given intravenously 40 ml (20g) gram/day for 7 days in MHE and overt HE. Blood ammonia levels decreased significantly in the group that received LOLA. Side effects obtained in 5% of the subjects, in the form of nausea and vomiting.[21] Poo (2006) examined 20 patients (10 cases and 10 controls) with liver cirrhosis and HE degree I-II, in which the case group received LOLA granules 9g/d for 2 weeks. The level of ammonia was decreased significantly in the group which received LOLA.[23] CFF increment in group A (2.4 Hz) was significantly greater (p=0.016) than

group B (0.7 Hz). This significant increment showed that there is an encephalopathy improvement in the group that received LOLA compared to the group that did not receive LOLA. This result supports the findings that have been raised by previous researchers.[21-23]

This study shows that an increase in prealbumin during nutritional improvement with LOLA is no better than nutritional improvement without LOLA. No research has been done to study the effects of LOLA in improving nutritional status in liver cirrhosis. LOLA actually has an indirect effect of nutritional improvement. One of the causes of decreased food intake in cirrhosis is encephalopathy. With the improvement in HE, it is expected that subsequently the food intake is also improved, which then followed by improvement of nutritional status. This study cannot prove that improved nutritional status is due to improvement in MHE because of short study period and the mean results of CFF after the intervention is still below 39 Hz making the patients still suffer encephalopathy. Within the period of 2 weeks it is less likely to find the effect of improved nutritional status through improved food intake.

In this study the safety of LOLA granules intake for 2 weeks is assessed, and found no significant difference between the mean increase in urea creatinine after the intervention and before intervention. These results indicate that the LOLA granules given for 2 weeks did not result in significant increase of urea–creatinine, although LOLA acts by increasing in the urea cycle.[25,35]

CONCLUSION

MHE with malnutrition can be given a diet of 35-40 cal / kgBW and 1.5 g protein/kgBW including BCAA substitution to improve nutritional status, and LOLA granules can be given to improve encephalopathy. Further studies are needed to assess more about the efficacy and side effects, with a better research design, larger sample size and longer duration of treatment.

REFERENCES

1. Kusumobroto HO. Sirosis hati. In: Sulaiman HA, Akbar HN, Lesmana LA, Noer HMS, eds. Buku ajar ilmu penyakit hati. 1st edition. Jakarta: Jayabadi; 2007. p. 335-45.
2. Kim WR, Brown RS, Terrault NA, El-Serag H. Burden of liver disease in the United States: Summary of workshop. Hepatol. 2002;36:227-42.
3. Sutocky J, Balasubramanian S. End stage liver disease (ESLD): Morbidity, mortality, and transplantation, California, 1999-2003. Department of health services California, 2005. Available from url:http://www.cdph.ca.gov/pubsforms/Pubs/OHIR endstageliver disease 1999-2003.pdf downloaded on 2008.
4. Sánchez MN, Ramírez JRA, Reyes A, Dehesa M, Juárez, A, Castañeda B. Etiology of liver cirrhosis in Mexico. Ann Hepatol. 2004;3:30-3.
5. Bajaj J. Management options for minimal hepatic encephalopathy. Expert Rev Gastroenterol & Hepatol. 2008;2:785-90.
6. Poordad FF. Review article: the burden of hepatic encephalopathy. Aliment Pharmacol Ther. 2006;25 (Suppl.1):3–9.
7. Riordan SM, Williams R. Treatment of hepatic encephalopathy. New Engl J Med. 1997;337:473-9.
8. Das A, Dhiman RK, Saraswat VA, Verma M, Naik SR. Chronic liver diasease: Epidemiology, patophysiology, diagnosis and treatment. Prevalence and natural history of subclinical hepatic encephalopathy in cirrhosis. J Gastroenterol and Hepatol. 2001;16:531-5.
9. Iskandar M, Ndraha S, Hasan I, Setiati S. Proporsi ensefalopati minimal pada pasien sirosis hepatis rawat jalan di RS Cipto Mangunkusumo. Kumpulan abstrak (CD) KOPAPDI: Jakarta; 2009.
10. Ndraha S, Hasan I. Critical flicker frequency pada sirosis hati di RSUD Koja. Kumpulan abstrak (CD) KOPAPDI: Jakarta; 2009.
11. Ortiz M, Jacas C, Co´rdoba J. Minimal hepatic encephalopathy: diagnosis, clinical significance and recommendations. J Hepatol. 2005;42:S45–S53.
12. Go´mez MR, Boza F, Valdecasas MSG, Emilio Garcý´a E, Reina JA. Subclinical hepatic encephalopathy predicts the development of overt hepatic encephalopathy. Am J Gastroenterol. 2001;96:2718–23.
13. P. Sharma, B.C. Sharma, V. Puri, S.K. Sarin. Critical flicker frequency: Diagnostic tool for minimal hepatic encephalopathy. J Hepatol 2007;47:67-73, doi:10.1016/j.jhep.2007.02.022. Available from url:http:/www.http://linkinghub.elsevier.com/retrieve/pii/S0 168827807001456 downloaded on 2008.
14. G´omez MR, C´ordoba J, Jover R, Olmo JA, Ramý´rez M, Rey R. Value of the critical flicker frequency in patients with minimal hepatic encephalopathy. Hepatol. 2007;45:879-85.
15. Kircheis G, Wettstein M, Timmermann L, Schitzler A, Häussinger D. Critical flicker frequency for quantification of low grade hepatic encephalopathy. Hepatol. 2002;35:357-66.
16. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei A. Hepatic encephalopathy – definition, nomenclature, diagnosis, and quantification: Final report of the working party at the 11th World Congress of Gastroenterology, Vienna, 1998. Hepatol. 2002;35:716-21.
17. Iskandar M, Ndraha S, Hasan I, Setiati S. Presisi ensefalopati minimal pada pasien sirosis hepatis rawat jalan di RS Cipto Mangunkusumo. Kumpulan abstrak (CD) KOPAPDI: Jakarta; 2009.
18. Norenberg MD, Jayakumar AR, Rama Rao KV, Panickar KS. The peripheral benzodiazepine receptor and neurosteroids in the pathogenesis of hepatic encephalopathy and amonia neurotoxicity. In: Häussinger, Kircheis G, Schliess F, eds. Hepatic encephalopathy and nitrogen metabolism. The Netherlands: Springer; 2006. p.143-59.
19. Henkel AS, Buchman AL. Nutritional support in patients with chronic liver disease. Nature Clin Pract Gastroenterol & Hepatol. 2006;3:202-9.

20. Kalaitzakis E, Olsson R, Henfridsson P, Hugosson I, Bengtsson M, Jalan R. Malnutrition and diabetes mellitus are related to hepatic encephalopathy in patients with liver cirrhosis. Liver Int. 2007;27:1194-201.
21. Kircheis G, Nilius R, Held C, Berndt H, Buchner M, Gortelmeyer R. Therapeutic efficacy of L-ornitine-L-aspartate infusions in patients with cirrhosis and hepatic encephalopathy: Results of a placebo-controlled, double-blind study. Hepatol. 1997;25:1351-60.
22. Grungreiff K, Baumann JL. Efficacy of L-ornitin L-aspartate granules in the treatment of chronic liver disease. Med Welt. 2001;52:219-26.
23. Poo JL, Gongora J, Avila FS, Castillo SA, Ramos GG, Zertuche MF. Efficacy of L-ornitin L-aspartate in cirrhotic patients with hyperammonemic hepatic encephalopathy. Results of a randomized, lactulose controlled study. Ann Hepatol. 2006;5:281-8.
24. Rees C J, Oppong K, Al Mardini H, Hudson M, Record C O. Effect of L-ornitine-L aspartate on patients with and without TIPS undergoing glutamin challenge: a double blind, placebo controlled trial. Gut. 2000;47:571–4.
25. Haussinger D. Nitrogen metabolism in liver: structural and functional organization and physiological relevance. Biochem. J. 1990;267:281-90.
26. Plauth M, Cabre´ E, Riggio O, Camilo MA, Pirlich M, Kondrup J. ESPEN Guidelines on enteral nutrition: liver diseases. Clin Nutr. 2006:25:285–94.
27. Freund H, Yoshimura N, Fischer JE. Chronic hepatic encephalopathy. Long-term therapy with a branched-chain amino-acid-enriched elemental diet. JAMA. 1979;242:347-9.
28. Plauth M, Egberts EH, Hamster W, Torok M, Muller PH, Brand O, Furst P, Dolle W. Long-term treatment of latent portosystemic encephalopathy with branched-chain amino acids. A double-blind placebo-controlled crossover study. J Hepatol. 1993;17:308–14.
29. Marchesini G, Dioguardi FS, Bianchi GP, Zoli M, Bellati G, Roffi L, Martines D, Abbiati R. Long-term oral branched-chain amino acid treatment in chronic hepatic encephalopathy. A randomized double-blind casein-controlled trial. The Italian Multicenter Study Group. J Hepatol. 1990;11:92–101.
30. Howell HW. Anthropometry and body composition analysis. In: Laura EM, Michele MG, eds. Contemporary nutrition support practice. A clinical guide. Philadelphia: WB Saunders Company;1998. p. 33-40.
31. Frisancho AR. New of upper limb fat and muscle areas for assessment of nutritional status. Am J Clin Nutr. 1981;34: 2540-5.
32. Beck FK, Rosenthal TC. Prealbumin: A marker for nutritional evaluation. Am Fam Physician. 2002;65:1575-8.
33. Devoto G, Gallo F, Marchello C, Racchi O, Garbarini R, Bonassi S. Serum concentrations as a useful tool in the assessment of malnutrition in hospitalized patients. Clin Chemist. 2006;52:2281–5.
34. Yovita H, Djumhana A, Abdurachman SA, Saketi JR. Correlation between anthropometrics measurements, prealbumin level and transferin serum with Child Pugh classification in evaluating nutritional status of liver cirrhosis patient. Acta Med Indones. 2004;36:197-201.
35. Merz Pharmaceuticals GmbH. Liver diseases and hepatic encephalopathy. Scientific product monograph. Frankfurt: Merz Pharmaceuticals GmbH; 2004. p.112-3.