The Efficacy of L-ornithine L-aspartate Granules and Normal Protein Diet in Minimal Hepatic Encephalopathy with Malnutrition

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ABSTRACT

Background: *The dietary protein restriction that was commonly recommended to hepatic encephalopathy (HE) patients, often leads to malnutrition, whereas malnutrition can deteriorate cirrhosis prognosis. The aims of this study were to find out encephalopathy improvement that was measured by critical flicker frequency (CFF) test and nutritional status by measuring prealbumin level after L-Ornithine L-Aspartate (LOLA) treatment with adequate calories and protein intake in patients with HE.*

Method: *Patients with liver cirrhosis who visited Cipto Mangunkusumo hospital on June-October 2009 was evaluated by CFF test using HEPAtonorm™ device. Encephalopathy was defined when CFF < 39 Hz. Nutritional status was measured by the mid-arm muscle circumference (MAMC) and was stated as malnutrition when the MAMC was below the 15th percentile. Patients had been treated by 3 x 6 mg LOLA granules for 2 weeks, and adequate calories and protein intake with branched-chain amino acid (BCAAs) substitution. The change of encephalopathy was evaluated by the CFF test and the nutritional status by measuring prealbumin blood level.*

Results: *There were 17 patients with liver cirrhosis who fulfilled the inclusion criteria. The mean CFF result increased from 34.1 ± 2.5 Hz to 36.5 ± 2.9 Hz after LOLA treatment with the adequate calories and protein intake including BCAAs substitution, which was statistically significant (p < 0.001) compared to before treatment. The prealbumin level also increased significantly compared before treatment, i.e. from 5.4 ± 2.1 mg/dL to 6.4 ± 2.6 mg/dL, p = 0.008.*

Conclusion: *HE patients with malnutrition could be given adequate calorie and protein with BCAAs substitution to improve their nutritional status, and LOLA granules for the improvement of HE.*

Keywords: *minimal hepatic encephalopathy, malnutrition, CFF, LOLA, prealbumin, BCAAs*

INTRODUCTION

Minimal hepatic encephalopathy (MHE) is a state of mental disturbance which cannot be diagnosed clinically but there is impairment with psychometric test.[1,2,3] MHE can have a far-reaching impact on the patient's quality of life, and also increases the risk of development of overt hepatic encephalopathy (HE).[4] MHE has difficulty being diagnosed because of the psychometric test is not easy to be carried out.[5,6]

Psychometric hepatic encephalopathy score (PHES) test has been used as the gold standard measurement for diagnosing MHE. However, such test is affected by age and education level.[7] Gomez et al found that the critical flicker frequency (CFF) test has a good validation to the PHES test. CFF test was easier, and less influenced by educational level of patients.[8] Study on precision of such test has been conducted in Jakarta, and these tests have obtained

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good precision.[9,10]

In liver cirrhosis, elevation of blood ammonia levels lead to increased number of peripheral benzodiazepines receptors (PBR), including the PBR in astrocytes and microglia in the brain. Furthermore, reactive oxygen species (ROS) also increased, followed by mitochondrial dysfunction, which resulted in the structure and function abnormalities in the brain astrocytes then lead into HE.[11] Since HE is due to increased blood ammonia level, protein intake was restricted in the management of HE. However, this would lead to malnutrition, which worsens the outcome of liver cirrhosis.[12,13]

Various studies have demonstrated that L-ornithine-L-aspartate (LOLA) can lower blood ammonia levels.[14-18] LOLA stimulates the urea cycle and glutamine synthesis, which is an important mechanism in the detoxification of ammonia.[19] With the efforts of LOLA, protein restriction is no longer needed to decrease blood ammonia levels. The European Society for Clinical Nutrition and Metabolism (ESPEN) recommended dietary of 35-40 kcal/kg/day and protein 1.2-1.5 g/kg/day for liver cirrhosis.[12] ESPEN also recommended the use of branched chain amino acids (BCAAs) to improve the nutritional status of patients with liver cirrhosis and malnutrition.[12,20]

Based on those issues, it is necessary to do research to find out whether LOLA could improve MHE in liver cirrhosis with malnutrition, even with adequate calories and protein intake.

The purposes of our study were: (1) To determine the improvement of CFF test; (2) Increasing of prealbumin level after intervention with LOLA and adequate calories and protein intake including BCAA substitution.

METHOD

This study was conducted in Cipto Mangunkusumo hospital and Koja hospital between June-October 2009, with a pre-test post-test design. It aimed to know the CFF test and prealbumin levels before and after LOLA treatment and the BCAA substitution to the MHE.

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.[21]

MHE was measured with HEPAtonorm™ analyzer, CFF < 39 Hz was considered to have encephalopathy.[5,6] Nutritional status 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).[22,23] Prealbumin was taken to assess the nutritional status improvement, performed with nephelometric technique, with normal value of 24.8-37.2 mg/dL.[24,25] The mean value of adequate calorie and protein intake with BCAA substitution was 35-40 kcal/kgBW and protein was 1.2-1.5 g/kgBW including hepatosol® 2 x 60 g, to reach the improvement of nutritional status.[12,13] Urea and creatinine levels before and after treatment were measured to evaluate the side effects on renal function.[26,27]

The inclusion criteria were liver cirrhosis patients with MHE (CFF test < 39 Hz) and malnutrition (MAMC below the 15th percentile). Subjects were excluded if there was acute infection, gastrointestinal bleeding, and 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. Afterwards, all subjects were given LOLA granules (hepamerz®) 3 x 6 g daily for 2 weeks. Then their prealbumin and CFF test were measured again. Statistical analysis conducted forpre-test post-test design was paired T-test or Wilcoxon test.

RESULTS

During the period of June - October 2009, we obtained 17 liver cirrhosis patients who meet the inclusion criteria (table 1). Ninety-four percent (16 subjects) were male and there was only 1 female patient. The mean age was 53.2 + 11.8 years, most subjects had a Child Pugh score B (91.2%). None of the subjects complained the side effects of BCAA or LOLA.

Table 1. Subject characteristics

Variable	n (%)	Mean ± SD
Sex		
Male	16 (94.1)	
Female	1 (5.9)	
Age (years)		53.2 ± 11.8
Hospital		
Cipto Mangunkusumo	10 (58.8)	
Koja	7 (41.2)	
Child Pugh		
B	15 (88.2)	
C	2 (11.8)	
Ammonia level (µmol/L)		146.9 (38)
Urea level (mg/dL)		22.8 (8.4)
Creatinine level (mg/dL)		0.8 (0.1)

Statistical analysis showed that mean value of CFF and prealbumin after LOLA and adequate calories and protein intake including BCAA was significantly higher than before treatment.

Table 2. Difference of mean value on CFF, prealbumin, urea, and creatinine level before and after treatment

	Before (mean ± SD)	After (mean ± SD)	Different (mean ± SD)	p†
CFF (Hz)	34.1 ± 2.5	36.5 ± 2.9	2.4 ± 1.6	< 0.001*
Prealbumin (mg/dL)	5.4 ± 2.1	6.4 ± 2.6	1 ± 1.3	0.008*
Urea (mg/dL)	22.8 ± 8.4	26.8 ± 7.6	4 ± 4.9	0.06
Creatinine (mg/dL)	0.8 ± 0.1	0.83 ± 0.1	0.03 ± 0.1	0.8

DISCUSSION

Result of statistical analysis showed improvement of CFF after treatment. Such significant improvement shows that LOLA can reduce plasma ammonia levels, so that diets with a normal content of protein can be administered safely to patients with hepatic encephalopathy.

It also can be seen that the provision of LOLA can improve MHE, and that the LOLA intake together with the improvement of nutrition are needed to overcome MHE on the malnourished liver cirrhosis patients. MHE improvement with such provision of LOLA is in accordance with Kircheis study and Poo.[14,16] However, study of LOLA in malnutrition liver cirrhosis with minimal encephalopathy is limited. In hepatic encephalopathy, protein intake was restricted in order to decrease blood ammonia level. But low protein intake could lead to malnutrition, and malnutrition will worsen the prognosis of liver cirrhosis.[13] Further studies are still needed to provide information that normal protein intake could be given in liver cirrhosis with malnutrition, without aggravation of hepatic encephalopathy.

Adequate calorie and protein on our subjects did not aggravate MHE, as measured by the CFF. This shows that the normal protein intake (1.2-1.5 g/kg) remains safe for MHE. The CFF indicates that the provision of normal protein may not worsen HE as proposed in earlier theories.[2,28] Normal proteins that do not aggravate the HE, has been suggested by previous researchers. Cordoba states that the normal protein can be given safely in liver cirrhosis with an episode of acute HE.[29] Gheorghe stated that for improvement of HE, protein restriction is not necessary.[30] The results obtained in our study reinforce findings from previous researchers.

Results of statistical tests showed that mean prealbumin level after adequate calorie and protein intake including BCAA substitution was significantly higher. The improvement of prealbumin in our study showed that patients had followed the dietary guidance. It assumed that patients who took adequate protein intake had increased blood ammonia level, but who took LOLAwould have reduced level. Therefore, no worsening of hepatic encephalopathy was seen.

Results of our study are in accordance with previous studies, which found that BCAA can improve the nutritional status of liver cirrhosis patients with malnutrition.[30] Muto and Nakaya have found improvement of serum albumin level in patients with advanced cirrhosis.[31,32]

Prealbumin is used as a parameter of nutrition improvement because it has a short half-life (2 days), so it is more sensitive to view changes in calorie-protein status and more accurately reflects the nutritional intake of current patient. It is supported by Beck, Devoto and Shenkin, which state that prealbumin is a practical examination and can be relied upon to assess the efficiency of nutritional intervention.[24,25,33]

Because LOLA works by stimulating urea cycle, elevation of blood urea levels can occurs. Therefore, in our study the safety of LOLA granules to urea and creatinine levels is evaluated after provision for 2 weeks.

From the mean posttest levels of urea, we obtained an increase of 4 mg/dL, but such increase was not clinically significant because it is still below the upper limit of normal values. In addition, the post-test creatinine level did not increase compared to the pre-test value. It strengthens the fact that renal function was not disrupted even though the production of urea increased.

CONCLUSION

The results of this study indicated that the mean of CFF test after giving LOLA with adequate calorie and protein intake including BCAA substitution are higher than before treatment. The mean levels of prealbumin after giving adequate calories and protein intake including BCAA substitution with LOLA are higher than before treatment.

Based on the study results, it can be recommended for patients with MHE and malnutrition to be treated with LOLA granules for improving their encephalopathy condition, and they can be given an adequate calories and protein intake including BCAA substitution to improve their nutritional status. Further studies are recommended to ensure the efficiency and drug side effects, with a better design, larger sample and longer time.

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