Alterations in Blood Ammonium Level and Psychometric Test in Patients with Liver Cirrhosis After a Tempe Diet

Neneng Ratnasari, Siti Nurdjanah

Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, University of Gadjah Mada/Dr. Sardjito Public General Hospital, Yogyakarta

ABSTRACT

Background

Hepatic encephalopathy is found in 50-70% cases of liver cirrhosis. Management of hepatic encephalopathy is based on the hypothesis of ammonia and false neurotransmitters. A vegetable diet is the diet of choice, since vegetable proteins have a high biological value, contains non-ammonigenic essential amino acids, and contains fiber. The results of soy fermentation by Rhizopus sp *can increase the nutritional value to make it easier for body digestion.*

Study aim

To determine improvements in hepatic encephalopathy by measuring the ammonium level and determining the psychometric test in patients with liver cirrhosis receiving a tempe diet compared to those receiving a liver diet (conventional diet).

Method

This is a random open clinical trial with a proportional stratification according to the Child Pugh criteria. Study subjects are patients with liver cirrhosis who are hospitalized at the Internal Medicine Ward and ambulatory patients at the out-patient Gastro-hepatology Polyclinic of Dr. Sarjito Public General Hospital, from January 1999 to May 2000. The trial was conducted for 20 days, where the first (trial) group was given a tempe diet, while the second (control) group was given liver diet II/III (conventional). Measured outcomes include peripheral blood ammonium level, and psychometric test using the Numeric Connection Test (NCT).

Results

In the first group, we found a significant reduction of ammonium level in Child-Pugh A patients and a non-significant reduction in Child-Pugh B/C patients, a non-significant psychometric test improvement in Child-Pugh A patients, and significant psychometric test improvement in Child-Pugh B/C patients. In group II: there is no significant difference in the changes in ammonium level or psychometric test in patients from both Child-Pugh categories.

Conclusion

A 20-day tempe diet can reduce ammonium levels and improve results on the psychometric test.

***Key words**: liver cirrhosis, hepatic encephalopathy, tempe diet, numeric connection test, Child-Pugh criteria*

INTRODUCTION

Hepatic encephalopathy is found in 50-70% of patients with liver cirrhosis.[3] Hepatic encephalopathy that occurs in liver cirrhosis is chronic in nature, and is also known as porto-systemic encephalopathy. It is a complex neuro-psychiatric syndrome characterized by depression of the central nervous system of various degrees, caused by hepatic insufficiency. It is a reversible abnormality.[4,5]

Chronic hepatic encephalopathy is characterized by reduced daily activity, reduced intellectual function, or psychomotor dysfunction, reduced EEG frequency, increased ammonium level, and abnormal psychomotor test results.[4,6] Most of patients with hepatic encephalopathy take the form of sub-clinical hepatic encephalopathy (no clinical mental or neurological abnormality, but abnormal psychometric test results). The prevalence varies from 30-84%, depending on the type of psychometric test and population. There is still no gold standard for the diagnosis of sub-clinical encephalopathy. There is an increased prevalence from Child Pugh A from 14% to 45%.[5,7]

The pathogenesis of chronic hepatic encephalopathy is as follows: there is an increase in amino acid transport through the blood brain barrier, increased cerebral energy metabolism, influence of neurotoxins produced by intestinal flora, changes in cerebral neurotransmitters, and other factors (mangan, H. pylori, and reduced cholin/creatinine ratio).[4]

There are two basic principles in the management of hepatic encephalopathy, which is generally based on the pathophysiological background, and is associated with the clinical type of encephalopathy (acute liver failure encephalopathy, liver cirrhosis with a trigger factor, chronic encephalopathy, and sub-clinical encephalopathy).[8] The study is conducted mainly based on the ammonia or false neurotransmitter hypothesis. Treatment based on the ammonia hypothesis comprises of reducing ammonia production (protein restriction, vegetable diet, carbohydrate enema, lactulose, oral lactytiol, and oral antibiotics), and increasing ammonia metabolism (ornithine aspartate, sodoum benzoate, phenylacetate, zinc supplementation). Therapy based on the false neurotransmitter hypothesis takes the form of administration of branched amino acid, levodopa, bromocriptine, flumazenyl, disodium calcium edentate, and sodium para-aminosalicyl acid.[3,4,5]

Tempe is a source of vegetable protein from the fermentation of soybean by rhizopus. The protein content after fermentation is better than prior to fermentation, since there is an increase in free fatty acid and the protein content is more easily absorbed. Tempe has been proven to be beneficial in reducing cholesterol, improving digestion, as well as anti-virus and anticancer agents.[9,10] Vegetable proteins contain little non-N- proteins, produces little ammonia, and is easily tolerated by the body. Proteins that greatly produce ammonia are glycine, serine, treonine, glutamine, hystidine, lysine, and aspargine (many of which are found in milk, eggs, and meat).[11,12]

There is very few studies on the effect of dietary regulation in patients with liver cirrhosis for prevention of hepatic encephalopathy. This study aims to determine improvements of hepatic encephalopathy by measuring the ammonium level and conduct psychometric testing on patients with liver cirrhosis receiving a tempe diet, compared to those receiving the conventional (liver) diet.

MATERIALS AND METHOD

The study was conducted in the Internal Department Ward and the Gastroenterology Polyclinic at Dr. Sardjito Public General Hospital, from January 1999 to May 2000. Study subjects were patients with liver cirrhosis diagnosed based on the Subandiri criteria and ultrasound examination. The study was conducted as an open clinical trial.

Inclusion criteria include: all patients with liver cirrhosis who are in stabile condition, living in the Yogyakarta Special Provincial Area. Exclusion criteria included: correction for bleeding (hematemesis/melena), renal failure (hepatorenal syndrome), severe infection, electrolyte imbalance, liver malignancy, precomatous conditions and hepatic coma. Patients that fulfilled the criteria were given an explanation on the aim and benefit of the study before they gave their consent and signed the informed consent form.

The degree of severity is based on the Child Pugh Criteria (A, B, and C) with laboratory evaluation (albumin, bilirubin, and prothrombine time), ascites, and the degree of hepatic encephalopathy. Ammonium evaluation is conducted using the amicheck meter II, and psychometric testing using the numeric connection test (NCT).

Study subjects were stratified into 2 groups, those in Child Pugh category A and those in categories B or C. Subjects from each category were randomized using a random table to determine the form of management. The first (trial) group in each category received a soy tempe diet (liver diet without meat proteins, with a protein requirement met from 30-40 grams of tempe per day). The second (control) group of each category was given (conventional) liver diet II/III (liver diet with meat and vegetable proteins). The tempe diet composition was as follows: rice/rice porridge, vegetables, 100 grams of soy tempe, fruits, 2 x 12.5 gram tempe milk (approximately 30-40 grams of protein). The second liver diet composition was as follows: rice porridge, vegetables, 50 grams of meat/25 gram of egg, and fruit (approximately 30 grams of protein). The third liver diet composition is as follows: rice/rice porridge, 100 gram

of meat/egg, 50 gram of tempeh, vegetables, and fruit (approximately 50 grams of protein).

The study was conducted for 20 days. During hospitalization, an expert nutritionist arranged the menu. When the patient was ready to be released, the tempe diet is continued at home in forms of the patient's preference, as long as it was in accordance with the liver diet. The patient is monitored every 3 days. To determine the dietary intake, there is a list to be filled by nutritionists or the patient's family. Medications for liver cirrhosis were continued.

The outcome measured was the ammonium level and psychometric test results (NCT). In addition to changes in the ammonium level (ug/dl) and the time required to complete the NCT test (in seconds), the ammonium level is evaluated using the ammonium level classification by Conn et al, 1984,[6] and classification of prolonged time based on Sanyal et al, 1994.[13] The data were managed using the computer program SPSS 6.0 for windows. Ammonium levels and NCT test results were displayed in the form of the mean and standard deviation, and were analyzed using the t test and two-tailed test. On the other hand, changes in ammonium level and prolonged NCT test were analyzed using the non-parametric (x2 test, *Wilcoxon matched-pair, signed rank test*). The significance limit was $p<0.05$.

RESULTS

Sixty-three patients with liver cirrhosis consented to participate in the study, 23 of which were classified as Child Pugh class A, 28 as Child Pugh class B, and 12 patients in Child Pugh class C. Based on the random table, the first (trial) group I consisted of 12 Child Pugh A patients, 13 Child Pugh B patients, and 6 Child Pugh C patients (with a total of 31 patients). The second (control) group consisted of 11 Child Pugh A patients, 15 Child Pugh B patients, and 6 Child Pugh C patients (with a total of 32 patients). The mean age of Child Pugh B/C patients in group I was 55.18 ± 10.8 years, and in group II was 56.17 ± 13.65 years. For Child Pugh A patients, the mean age was 54.73 ± 10.20 years for group I and 53.45 ± 12.94 years for group II. There were 4 patients excluded from the study, since 1 patient from the first group of Child Pugh A patients suffered from bleeding (hematemesis), while 3 patients had a worsened condition (1 from Child Pugh C group II, 1 from Child Pugh B group I, and 1 from Child Pugh C group I).

Table 1 demonstrates the results of ammonium level and psychometric test (NCT) for each category and group at the beginning (initial point) and at the end (final point) of the study. The mean initial ammonium level in group I Child Pugh A was 181.36 ± 64.48 ug/dl, while the final ammonium level was 135.27 ± 42.10 ug/dl. This demonstrates a significant reduction with a p of 0.0030. The average ammonium level in group II Child Pugh A was 152.0 ± 42.41 ug/dl, while the final ammonium level was 170.55 ± 48.41 ug/dl, demonstrating no significant change (p=0.378). The average initial psychometric test (NCT) in group I Child Pugh A patients was 44.55 ± 16.79 seconds, while at the end of the study (the final results) was 39.00 ± 9.89 seconds, demonstrating no significant change (p=0.114). The mean initial psychometric test results (NCT) group II Child Pugh A was 49.18 ± 18.90 seconds, while the final results was 45.09 ± 24.25 seconds, demonstrating no significant change (p=0.594).

Table 1. Ammonium Level and Psychometric Test Results (NCT) and Liver Cirrhosis Patients Group I (trial) and Group II (control)

	Group I			Group II		
	Initial	Final	Σ	Initial	Final	p Σ
	(δ)		(CI 95%)	(δ)		(CI 95%)
CP A						
- Amonia	181,36±64,48	135,27±42,1	0,030* 11	152,0±42,4	170,55±48,41	0,379 11
	(-46,09±60,56)		(5,394;86,788)	(25,27±64,15)		(-63,318;26,227)
- NCT	44,56±16,79	39,0±9,89	0,114	49,18±18,9	45,09±24,25	0,594
	(-6,45±9,72)		(-1,581;12,672)	(-2,64±24,78)		(-12,466;20,648)
CP B/C						
- Amonia	216,88±77,15	183,0±48,1	0,113 17	277,05±65,6	217,25±88,22	0,163 20
	(-34,41±83,36)		(-1,78±91,76)	(-13,213;72,813)		
- NCT	105,29±68,99	76,94±45,75	0,004*	109,35±64,54	97,9±68,18	0,075
	(-28,35±35,17)		(10,263;46,442)	(-8,28±25,97)		(-1,261;24,161)

* p<0,05

The mean ammonium Child Pugh B or C group I was 216.88 ± 77.65 ug/dl at the beginning of the study (the initial level) and 183.0 ± 48.10 ug/dl at the end of study (the final level), without any significant change (p=0.113). The mean ammonium of Child Pugh B or C group II was 247.05 ± 65.60 ug/dl at the beginning of the study (the initial level), and 217.25 ± 88.22 seconds at the end of the study (the final level), without any significant change (p=0.163). The mean psychometric test (NCT) of the group I in Child Pugh B and C was 105.29 ± 68.99 seconds at the beginning of the study (the initial level) and 105.29 ± 64.54 seconds at the end of the study (the final level), demonstrating a significant change (p=0.004). The mean NCT test results of group II Child Pugh B or C was 109.35 ± 64.54 seconds at the beginning of the study (the initial level) and 97.9 ± 68.18 at the end (the final level), demonstrating no significant change (p=0.075) (Table 1).

Changes in the ammonium level based on the classification of ammonium level in Group I Child Pugh class A patients demonstrated a significant change (p=0.043, z=-2.0284), where at the beginning of the study 36% (4) were at the level zero, 18.2% (2) were at level 1, 27.3% (3) were at level 2, and 18.2% (2) were at level 3; while at the end of the study the number changed to 63.6% (7) for level 0 and 36.4% (4) at level 1, while for group 2 Child Pugh cases there was no significant change (p=0.314, z=-1.007) (Table 2). In Child Pugh B/C patients, there was no significant change (p>0.05) in the two groups. (Table 2)

There was no significant difference in the change in the time needed to finish the psychometric test in patients with Child Pugh A patients according to the classification (levels) in each group (p>0.05). While in the first group of Child Pugh B/C patients there was a significant difference (p=0.018; z=-2.3664). At the beginning of the study, there were 29.4% (5) in level 0; 17.6% (3) in level 1; 5.9% (1) in level 2; 11.8% (2) in level 3, and 35.3% (6) in level 4, while at the end of the study, there were 41% (7) in level 0; 5.9% (1) in level 1; 11.8% (2) in level 2; 35.3% (6) in level 3; and 5.9% (1) in level 4. While in group II, no significant change was found (Table 3).

Table 2. Changes in Ammonium Level in Group I (trial) and Group II (control) Patients With Liver Cirrhosis

Level (ug/dl)	Child Pugh A				Child Pugh B/C			
	Group I (11)		Group II (11)		Group I (17)		Group II (20)	
	Initial (%)	Final (%)	Initial (%)	Final (%)	Initial (%)	Final (%)	Initial (%)	Final (%)
0(≤150)	4(36,4)	7(63,6)	6(54,4)	5(45,4)	4(23,5)	3(17,6)	-	3(25)
1(151-200)	2(18,2)	4(36,4)	4(36,4)	3(27,3)	2(11,8)	9(52,9)	5(25)	6(30)
2(201-250)	3(27,3)	-	1(9,1)	3(27,3)	7(41,2)	4(23,5)	5(25)	4(20)
3(251-300)	-	-	-	-	2(11,8)	1(5,9)	6(30)	3(15)
4(>300)	-	-	-	-	2(11,8)		4(20)	4(20)
	z=-2,0284 p= 0,0043*		z=-1,007 p= 0,314		z=-1,5115 p= 0,131		z=-1,5724 p= 0,116	

* p<0,05

Table 3. Changes In Psychometric Test Results In Group I (trial) and Group II (control) Patients With Liver Cirrhosis

Level > time# (second)	Child Pugh A				Child Pugh B/C			
	Group I (11)		Group II (11)		Group I (17)		Group II (20)	
	Initial (%)	Final (%)	Initial (%)	Final (%)	Initial (%)	Final (%)	Initial (%)	Final (%)
0(≤15)	7(63,6)	8(672,7)	6(54,5)	7(63,6)	5(29,4)	7(41,2)	3(15)	5(25)
1(15-30)	1(9,1)	3 (27,3)	2(18,2)	3(27,3)	3(17,6)	1(5,9)	3(15)	2(10)
2(31-60)	3(27,3)	-	3(27,3)	-	1(5,9)	2(11,8)	4(20)	4(20)
3(61-120)	-	-	-	-	2(11,8)	6(35,3)	5(25)	5(25)
4(>120)	-	-	-	-	6(35,3)	1(5,9)	5(25)	4(20)
	z=-1,1351 p= 0,249		z=-0,5394 p= 0,590		z=-2,3664 p= 0,018*		z=-1,6903 p= 0,091	

* p<0,05
#NCT test time counts with prolonged time in 30 second.

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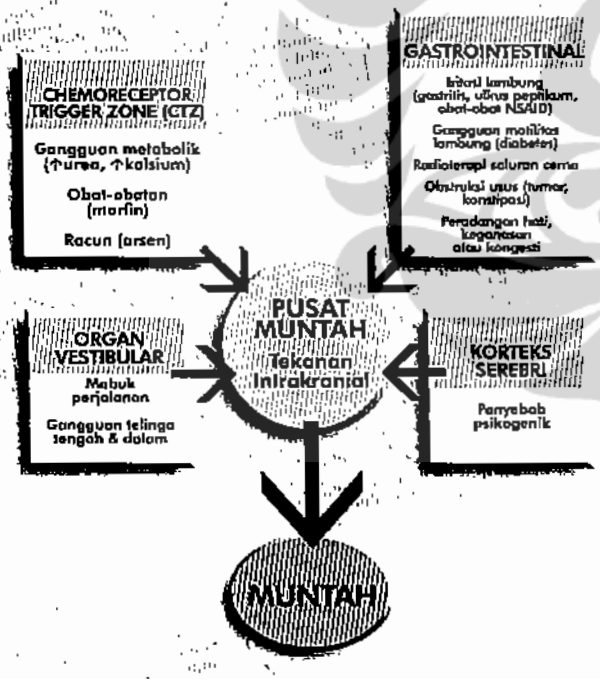

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DISCUSSION

The prevalence rate of hepatic encephalopathy reported to the Department of Internal Medicine at Dr. Sardjito Public General Hospital was 11.7%, with bleeding as the main cause.[14] In abroad, hepatic encephalopathy has not been completely evaluated, and study had only been conducted on factors supporting the hypothesis for hepatic encephalopathy, which are increased ammonium levels and abnormal psychometric testing unaccompanied by EEG evaluation. A similar study with long term AARC supplement has also been performed.[6]

According to the study on 20-day tempe diet, there was a significant reduction of ammonium level in Group I Child Pugh A patients. Such results were in line with the ammonium level ($z = -2.0284$; $p = 0.043$). Improvements in psychometric testing do not demonstrate a significant change, probably because in the two groups for Child Pugh A, most of the results of the NCT test at the beginning of the study was level 0, at 63.6% (group I), and 54.5% (group II).

The mean reduction in ammonium level in the first group of Child Pugh B/C patients was 34.41 ± 83.36, while in the second group it is 1.78 ± 91.76. But in the two groups, the reduction did not show a significant difference ($p>0.005$). Improvements in the psychometric test in group I Child Pugh B/C demonstrated a significant reduction to 28.35 ± 35.17 seconds, $p=0.004$, while in the second group there was no significant improvement. This was also supported with improvements in test results based on the level ($z = -2.3664$; $p = 0.018$).

During the study, there were no complaints (diarrhea, constipation, and vomiting). Only several patients complained of nausea and vomiting after drinking the tempe milk, due to an unpleasant aroma. Most patients feel better after consuming a tempe diet. The limitations of this study is as follows: inability to control other dietary intake, different ability of patients to finish their tempe diet, boredom towards a tempe diet after the patient returns home, and limitations in instruments, money, and time for the study.

CONCLUSION

Based on the study results we could conclude that administration of a tempe diet for 20 days in patients with liver cirrhosis:

1. Could significantly reduce the ammonium level in Child Pugh A patients and was not significant in Child Pugh B or C compared to patients receiving the (conventional) liver diet.
2. Was able to significantly improve the time needed for the psychometric test in patients with Child Pugh B or C compared to Child Pugh patients B or C receiving the (conventional) liver diet.

SUGGESTION

There are still need more specific study with double blind method. For anticipate study bias, the diet tempe with consider the quality of tempe is needed for that study.

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