

Comparison of the Effectiveness in Administration of Lactulose, Probiotics and a Combination of Lactulose and Probiotics against Hepatic Encephalopathy in Patients with Liver Cirrhosis

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Abstract : Hepatic Encephalopathy (HE) is one of the most common complication of decompensated liver cirrhosis. In chronic liver disease there will be a disruption of ammonia metabolism resulting in an increase of 5-10 times ammonia levels which will disrupt the physiology of the brain and brain metabolism. Treatment with lactulose and probiotics can provide benefits in improving hepatic encephalopathy. The research subjects were divided into three groups: group A consisted of 17 people receiving 30-60ml/day lactulose, group B received one capsule probiotic taken three times per day (each capsule containing 2 billion of *Lactobacillus acidophilus* Rosell-52, 2 billion of *Lactobacillus rhamnosus* Rosell-11 2, 211 mg of Maltodextrin, 8mg of Magnesium stearate and 1 mg of ascorbic acid) and group C received both lactulose and probiotics. In our study, we found that there was an improvement in the degree of Hepatic Encephalopathy from severe HE to mild HE in two people (40%) from group A and one person (50%) from group C with $p > 0.05$.

1 INTRODUCTION

Liver cirrhosis is an end-stage progressive hepatic fibrosis characterized by distortion of hepatic architecture and regenerative nodule formation (Nurjannah S, 2009). The Indonesian Liver Research Association known as Perhimpunan Peneliti Hati Indonesia (PPHI) stated that the prevalence of patients with liver cirrhosis is 3.5% of all patients treated in internal medicine inpatient unit, or an average of 47.4% of all liver disease patients treated (PPHI-INA ASL., 2013).

Hepatic Encephalopathy (HE) is one of the most common complication of decompensated liver cirrhosis. It is a neuropsychiatric syndrome found in patient with both acute and chronic liver failure. The clinical features are mental disorders, neurological disorders, presence of liver parenchymal abnormalities and laboratory abnormalities. HE is caused by the failure of hepatocellular function, decreased ability of the liver to detoxify ammonia and other toxins along with a portosystemic shortcut causing toxic materials to enter the systemic blood and brain directly without previously being cleaned in the liver (Zubir N, 2009).

Lactulose has laxative characteristics causing a decrease in the synthesis and uptake of ammonia

by decreasing colon pH and also reducing glutamine uptake. Lactulose is converted into monosaccharide by normal flora and used as a food source so that the growth of normal intestinal flora will suppress other bacteria that produce urease. This process produces lactic acid and also gives hydrogen ions to ammonia so that the molecules change from ammonia (NH_3) and become ammonium ions (NH_4^+). The presence of this ionization attracts ammonia from the blood towards the lumen (Nielsen B *et al*, 2004; Luo M *et al*, 2011). Sharma *et al* (2011) and Watanabe *et al* (1997) found that lactulose is effective in preventing HE in patients with liver cirrhosis and upper gastrointestinal bleeding.

Probiotics are defined as non-pathogenic living microorganisms, which if consumed in a certain amount will give beneficial effects for the host. Ammonia is also produced by flora in the intestine so that manipulation of intestinal flora is one of the HE therapy strategies. Probiotics given to HE patients can reduce total ammonia in the portal blood by decreasing bacterial urease activity, decrease absorption of ammonia by decreasing pH, decrease intestinal permeability and increase nutritional status of intestinal epithelium and reduce inflammation caused by oxidative stress in hepatocytes thus increasing hepatic clearance of

ammonia and toxins and reducing toxin uptake (Saji S *et al.*, 2011; Bousvaros A *et al.*, 2005).

Several studies have shown that lactulose and probiotics have good ability to prevent the recurrence of hepatic encephalopathy and significantly show improvement in psychometric tests in patients with mild hepatic encephalopathy. This is the underlying purpose to compare the effectiveness between the administration of lactulose, probiotics and the combination of lactulose and probiotics to patients with liver cirrhosis and hepatic encephalopathy.

2 PATIENTS AND METHODS

2.1 Research Methods

Clinical trials with paired categorical analytic studies was carried out in the internal medicine inpatient unit at Dr. Zainoel Abidin Hospital in Banda Aceh. The study samples were taken from patients who were diagnosed with decompensated cirrhosis with hepatic encephalopathy and fulfilled the inclusion and exclusion criterias (diarrhea, using alcohol ≥ 20 g/day, decreased level of consciousness caused by other conditions than HE, having spontaneous bacterial peritonitis for the past 6 weeks, and taking antibiotics such as Neomycin, Metronidazole and Rifaximin).

The diagnosis of decompensated liver cirrhosis is based on medical history, physical examination, laboratory findings and abdominal ultrasonography. The research subjects were taken by consecutive sampling, then all research subjects were carried out simple randomization with a random table system and subjects were allocated into three groups: A, B, and C. Group A was given lactulose 30-60 ml per day until the patients secreted soft defecation 2-3 times per day. Group B was given one capsule probiotics three times per day (each capsule containing 2 billion of *Lactobacillus acidophilus Rosell-52*, 2 billion of *Lactobacillus rhamnosus Rosell-11*, 211 mg of Maltodextrin, 8 mg of Magnesium stearate and 1 mg of ascorbic acid). And group C received both lactulose and probiotics. The therapy is carried out for two weeks.

Ammonia examination using an ammonia test kit was done by taking capillary blood from the patient's fingertip as much as 20 μ l, dropping it in the reagent then inserting it into the device, the results were read in μ g/dl after 3 minutes.

Ethical clearance was obtained from the Ethics Committee of the Faculty of Medicine, Syiah Kuala University.

2.2 Operational Definition

Liver cirrhosis is diagnosed based on medical history, physical examination, laboratory findings and upper abdominal ultrasonography. Hepatic encephalopathy is a disorder of cognitive function in patients with liver disease that cannot be identified only with complete medical history and neurological examination including family member interviews. To diagnose hepatic encephalopathy, we need to find some abnormalities from neuropsychometric or neurophysiological tests using NCT A/B and West Haven criteria. In this study, HE degrees were measured using West Haven criteria. Ammonia is a major factor in the pathogenesis of hepatic encephalopathy. Increased ammonia levels can be due to high protein intake, constipation, gastrointestinal bleeding, infection, azotemia, hypokalemia. Normal level of blood ammonia is 0-150 μ g/dl.

2.3 Statistical Analysis

Statistical analysis was carried out by computerization, with a significance level of $p < 0.05$. Normal data distribution was analysed by *repeated anova* test and continued with *Bonferroni post-hoc* analysis to find out which groups have significant result.

3 RESULTS

The research subjects were divided into three groups: 17 people in lactulose group, 17 people in probiotic group and 17 people in lactulose + probiotic group. During the research two people from the lactulose + probiotic group resigned. The number of subjects that followed the research until the end were 49. The lactulose group received standard cirrhosis therapy plus lactulose 30-60 ml/day, the probiotic group received standard cirrhosis therapy plus probiotics 1 capsule 3 times per day (each capsule containing 2 billion of *Lactobacillus acidophilus Rosell-52*, 2 billion of *Lactobacillus rhamnosus Rosell-11*, 211 mg of Maltodextrin, 8 mg of Magnesium stearate and 1 mg ascorbic acid), while the third group received both lactulose and probiotics. The study was conducted for two weeks and the parameters assessed were

ammonia level in the blood and the degree of hepatic encephalopathy. Before the study begins, all subjects were examined for hepatitis B and C markers, endoscopy examination, albumin level, bilirubin level and liver function. We found that all the basic characteristics in the subjects were the same in the three groups.

Table 1. Basic Characteristics of The Subjects.

Variable	Groups			P
	Lactulose (n=17)	Probiotics (n=17)	Lactulose +Probiotic (n=15)	
Age (years)	53,11±12,81	56,41±12,97	57,86±17,42	p >0,05
Gender				
Male	10(29,4%)	12(35,3%)	12(35,3%)	
Female	7(46,7%)	5(33,3%)	3(20,0%)	
Liver cirrhosis Etiology				
HBV	7(25,0%)	12(42,9%)	9(32,1%)	p >0,05
HCV	1(25,0%)	1(25,0%)	2(50,0%)	
Non B dan C	9(52,9%)	4(23,5%)	4(23,5%)	
HE degree (%)				
Mild	12(30,8%)	14(35,9%)	13(33,3%)	p >0,05
Severe	5(50,0%)	3(30,0%)	2(20,0%)	
Endoscopy (%)				
VE	12(42,9%)	6(21,4%)	10(35,7%)	p >0,05
PHG	3(50,0%)	3(50,0%)	-	
VE/PHG	2(13,3%)	8(53,3%)	5(33,3%)	
Albumin (g/dl)	2,50±0,43	2,55±0,61	2,46±0,43	p >0,05
Bilirubin (mg/dl)	6,15±8,23	3,21±2,39	4,16±6,18	p >0,05
SGOT (U/l)	146,35±97,99	133,94±87,71	113,33±68,4	p >0,05
SGPT (U/l)	92,94±66,21	94,82±73,87	91,80±63,77	p >0,05
Ammonia (ug/dl)	198,29±21,44	197,35±22,20	188,53±26,0	p >0,05

HBV = Hepatitis B Virus, HCV = Hepatitis C Virus, HE = Hepatic Encephalopathy, VE = Varices Esophagus, PHG = Portal Hypertension Gastropathy, SGOT = Serum Glutamic Oxaloacetic Transaminase, SGPT = Serum Glutamic Piruvic Transaminase

There was a decrease in ammonia level in average in all three groups around 194.97 ± 16.05 ug/dl. The reduction in ammonia level in each group was statistically significant. But the difference between the ammonia levels in the three groups is 8.59 ug/dl which is not statistically significant (p> 0.05).

Table 2. Ammonia level in three groups before and after two weeks of therapy

Groups	Ammonia levels before therapy (ug/dl)	Ammonia levels after two weeks of therapy (ug/dl)	P
Lactulose	198,29±21,44	136,11±19,99	p< 0,05
Probiotic	197,35±22,20	143,76±29,73	p < 0,05
Lactulose+ Probiotic	188,53±26,04	129,93±22,4	p < 0,05

There was an improvement in the degree of hepatic encephalopathy from severe HE to mild HE in two people from group A (40%) and one person from group C (50%). The improvement in HE degree was not statistically significant (p> 0.05).

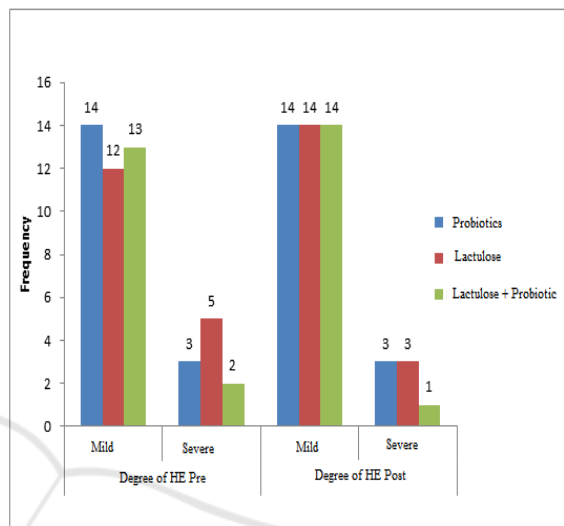


Figure 1. The change in the Hepatic Encephalopathy degree before and after two weeks of therapy in the three groups.

4 DISCUSSION

Based on this study, there was a significant reduction in ammonia level in the blood after two weeks of therapy in the three groups. Lactulose can reduce ammonia levels in the blood and improve the results of psychometric tests thus affect the quality of life of patients with liver cirrhosis who experienced HE. The results of this study are consistent with the study of Nie et al in 2003, who conducted a study of lactulose administration for 8 to 28 weeks in patients with liver cirrhosis who had hepatic encephalopathy. There was reduction in ammonia levels in the blood, improved psychometric tests and prevention of recurrent encephalopathy (Nie YQ *et al*, 2003).

In 2011, Saji S et al. conducted a study by administering probiotics to 21 patients with liver cirrhosis who had been diagnosed with hepatic encephalopathy for at least 6 months. The results showed that ammonia levels decreased from 140.29 ± 7.28 to 122.38 ± 10.69 and there was a significant decrease in the second and third days compared to the first day. Probiotics can reduce blood ammonia levels by increasing the concentration of non-urease

bacteria and acting as a beneficial agent for the balance of intestinal flora (Pawar RR *et al*, 2012).

In 2000, Dhiman *et al.* conducted a study by administering lactulose for 3 months in subclinical patients with hepatic encephalopathy. After that, they performed NCT examination, FCT, *block design* and *picture assembly*. And later, they found some improvements in psychometric tests and minimal hepatic encephalopathy.

In 2014, Shavakhi *et al.* administered probiotics and lactulose to liver cirrhosis patients with mild hepatic encephalopathy for 2 weeks and 8 weeks follow-up. They found that lactulose and probiotics were effective for minimal improvement of hepatic encephalopathy. In comparison, probiotics are superior to lactulose in improving hepatic encephalopathy.

This study had several limitations. Firstly, the number of samples was relatively small thus there can be a bias in processing. Secondly, the examination of hepatic encephalopathy only used West Haven criteria, so we cannot assess the changes in the degree of mild hepatic encephalopathy to non-hepatic encephalopathy which can be confirmed by a more accurate examination such as Critical Flicker Frequency (CFF). Thirdly, the limited time for the research made us unable to observe the long term side effect of lactulose and probiotics administration.

5 CONCLUSIONS

Administering lactulose, probiotics and a combination of both probiotics and lactulose have the same effectiveness in reducing ammonia levels in the blood, as well as decreasing HE degree from severe to mild degree.

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