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Efficacy of Lactulose in Cirrhotic patients with Subclinical Hepatic Encephalopathy (SHE)

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ABSTRACT

Background: Subclinical Hepatic Encephalopathy (SHE) is a subclinical syndrome of neuropsychological and neurophysiological deficit in patients with liver disease that cannot be detected by routine clinical testing.

Objective: To study the efficacy of lactulose for the treatment of cirrhotic patients with SHE.

Patients and Methods: A total of 91 cirrhotic patients, 50 males and 41 females were included in this study. The majority 92.3% were CTP class A and 7.69% class B; age 32-82 years old. The diagnosis of SHE was made by electroencephalogram (EEG) and quantitative psychometric test [Number Connection Test (NCT), Digit Symbol Test (DST) and Block Design Test (BDT)]. Abnormalities at least 2/3 of psychometric tests or abnormal EEG findings were the criteria used for diagnosis of SHE.

Results: Thirty (27.3%) patients were diagnosed as SHE; 10 patients were excluded from the study because five were not cooperative, four deteriorated from HE, and one died from severe cellulitis with septic shock. Out of 30 patients with SHE, only 20 were recruited in the study. Double-blind randomized study on the efficacy of lactulose vs placebo in 20 SHE patients was conducted; 11 were randomized to treatment group (lactulose 30-45 ml/day for 2 months) and 9 to placebo group (placebo 30-45 ml/day for 2 months). Psychometric tests and EEG were performed in all patients in both groups after two months. Improvement of psychometric test, BDT, was 4 (36.3%) in the treatment group and 4 patients in the placebo group (44.4%) ($p = 0.192$). Improvement of DST was 4 (36.3%) in the treatment group and 3 patients in the placebo group (33.3%), ($p = 1.000$). Mean NCT time pre and post treatment in the treatment group and placebo were $145.9 \pm 79.5 : 167 \pm 164.8$ sec and $115.7 \pm 71.8 : 102.4 \pm 65.5$ sec ($p = 0.302$), respectively. EEG improvement in the treatment group was 2 (18.1%) compared to none in the placebo group, ($p = 0.479$).

Conclusions: For cirrhotic patients with SHE, lactulose was not able to improve psychometric tests and EEG.

Key words : Lactulose, subclinical, hepatic encephalopathy

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BACKGROUND

In patients with cirrhosis, hepatic encephalopathy (HE) is one of the common complications. Clinical manifestations of HE include intellectual function deterioration, personality disorders, altered level of consciousness and neuromuscular dysfunction.[1] HE has been graded into 4 stages of severity, ranging from attention deficits to coma.[2] In addition to clinical manifested HE, patients without overt HE may be described as subclinical or minimal HE, which cannot be detected by routine physical examination, but can be diagnosed by using neuropsychological or neurophysiological tests.[3-12] The prevalence of SHE varies from 30-70% of cirrhotic patients and is considered to be clinically relevant for many reasons such as it could be a preceding stage of clinical manifest HE and impaired quality of life including influence on patients' daily functioning e.g.,driving a car or performing at work.[13-18] Therefore, it is important to detect this condition and plan for a long term management of cirrhotic patients to understand the presence of SHE and to pay attention for changes in daily behavior and sleep.

Lactulose has been used worldwide for the treatment of overt HE since 1966 along with low protein diet.[19] In this study, we examined whether lactulose administration at a conventional dose was beneficial in cirrhotic patients with SHE.

PATIENTS AND METHODS

From March to November 2005, a total of 91 consecutive outpatients with hepatic cirrhotic CTP class A and B from medicine OPD and GI clinic at Ramathibodi Hospital were enrolled to screen for SHE. Diagnosis of cirrhosis was made by history taking, blood chemistry, imaging and/or liver histology. Inclusion criteria were all cirrhotic CTP A and B patients from any causes, age between 20-85 years with proven no neurological or mental disease, no clinical overt HE during the past 2 months and no sedative or other psychotropic drugs use within two weeks prior to the tests. Exclusion criteria were clinical overt HE, history of alcohol consuming >40 g/day within 1 week prior to the study, history of recent (less than 4 weeks) gastrointestinal bleeding, history of portosystemic shunt operation, anemia, dehydration or electrolyte imbalance, fever, presence of severe cardio pulmonary or renal or cerebrovascular discase including DM and inability to perform EEG and/or psychometric tests. SHE[20] was assessed by using both neurophysiological test electroencephalogram: EEG) and quantitative psychometric tests that included the Number Connection Test (Trail making test-A) (NCT-A), and two performance subtests of the Wechsler Adult Intelligence Scale (Revised) (WAIS-R), Digit Symbol Test (DST) and Block Design Test (BDT).[21,22] SHE was defined as the presence of at least two abnormal psychometric tests or abnormal slowing of the EEG. All of the test results were assessed according to the normal values from WAIS-R. The NCT-A was considered abnormal when the time taken was greater than 30 seconds. A DST test and a BDT test result value outside 2 standard deviation are considered abnormal. The EEG was recorded using standardized techniques. A theta activity above 35% by EEG was considered abnormal.

Cirrhotic patients with SHE who fit the selection criteria for this study were randomized into two groups: treatment group and placebo group. In the treatment group, patients were given lactulose 30-45 ml/day once daily before bedtime for 2 months so that each patient could pass two to three semisoft stools per day. In placebo group, patients were given placebo 30-45 ml/day once daily before bed time for 2 months. Concomitant medications (including drugs used for the treatment of complications of cirrhosis or conditions other than cirrhosis) were continued with minimal changes in the dose, but the use of drugs that were considered to have direct effects on HE, such as branched-chain amino acid preparations and nonabsorbable antibiotics, was prohibited in principle. The patients were allowed to have their routine daily activities including eating behavior.

At week 4 and at the end of treatment protocol, patients were asked to visit GI clinic to have physical examination for detection of clinical manifest of overt HE. All patients in both groups had to repeat all 3 psychometric tests and EEG after the completetion of lactulose or placebo treatment (2-month period) Drug compliance and side effects were observed in each patient by phone at week 2 and 6 of the treatment.

Informed written consent was obtained from each subject. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approved by the Research Ethics Committee of Ramathibodi Hospital, Mahidol University, Thailand.

Statistical analysis

The results were expressed as the mean ± SD. All statistical analyses were performed using chi square test, t-test and Ranksum test for comparison of proportion, mean and median between lactulose and placebo group, respectively. P <0.05 was considered as statistically significant.

RESULTS

A total of 91 cirrhotic patients (50 males and 41 females), majority (92.3%) of the patients, was in CTP class A and the rest was in CTP class B, age between 32-82 years old, were eligible for the study. SHE was diagnosed in 30 (27.3%) of 91 patients. Ten patients were excluded from the study because 5 patients were not cooperative, 4 patients deteriorated form overt HE and 1 patient died from severe cellulitis of the left leg with septic shock.

In the final analysis, 20 patients, mean age 57 ± 9.1 years, were double blind randomized into 2 groups. Eleven patients were randomized to lactulose group and 9 patients to placebo group. Both groups were compared in relation to their clinical characteristics (Table 1).

Significant differences between lactulose and placebo group were observed in prothrombin time and INR (P = 0.043 and 0.034, respectively). For other variables such as age, sex, CTP score, ascites, bilirubin, serum albumin and arterial ammonia, were not statistically significant between both groups.

Etiologies of cirrhosis in lactulose group were alcohol, HCV, HBV and NASH which represented 36.4%, 27.3%, 27.3% and 9.1%, respectively. HCV (33.3%), alcohol (22.2%), cryptogenic (22.2%), HBV (11.1%) and hemochromatosis (11.1%) were reported as the causes of cirrhosis in placebo group (Figure 1). There were no statistical significance between both groups.

Neurophysiological test results

EEG was abnormal in 3 patients in the lactulose group and none in placebo group. At the end of treatment (2 months) with lactulose and placebo, EEG

Table 1 General Characteristics of Populations in Each Group

General Characteristics	Lactulose N (%)	Placebo N (%)	P-value
Age (mean/yr)	57.4 ± 7.6	56.5 ± 11.2	P = 0.850
Sex- Male: Female	2:9 (18.2 : 81.8%)	4:5 (44.4 : 55.6%)	P = 0.336
CTP A:B	10:1 (90.9:9.1%)	8:1 (88.9:11.1%)	P = 0.811
Ascites	1 (9.1:%)	0 (0%)	P = 1.00
Bilirubin (mean:mg/dl)	1.4 ± 0.6	1.3 ± 1.0	P = 0.818
Serum albumin (mean:g/dl)	3.6 ± 0.5	3.9 ± 0.5	P = 0.168
Prothrombin time (mean:second)	15.2 ± 2.5	13.2 ± 1.3	P = 0.043
INR (mean)	1.3 ± 0.2	1.1 ± 0.1	P = 0.034
Arterial ammonia (median/min, max:ug/dl)	110.5 (19-172)	116 (43-168)	P = 0.68

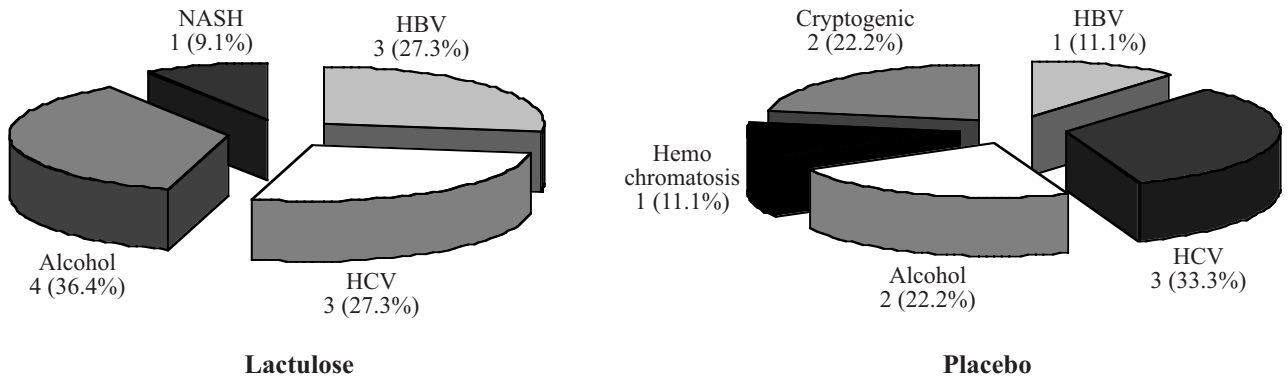

Figure 1 Diagram demonstrating causes of cirrhosis in both groups

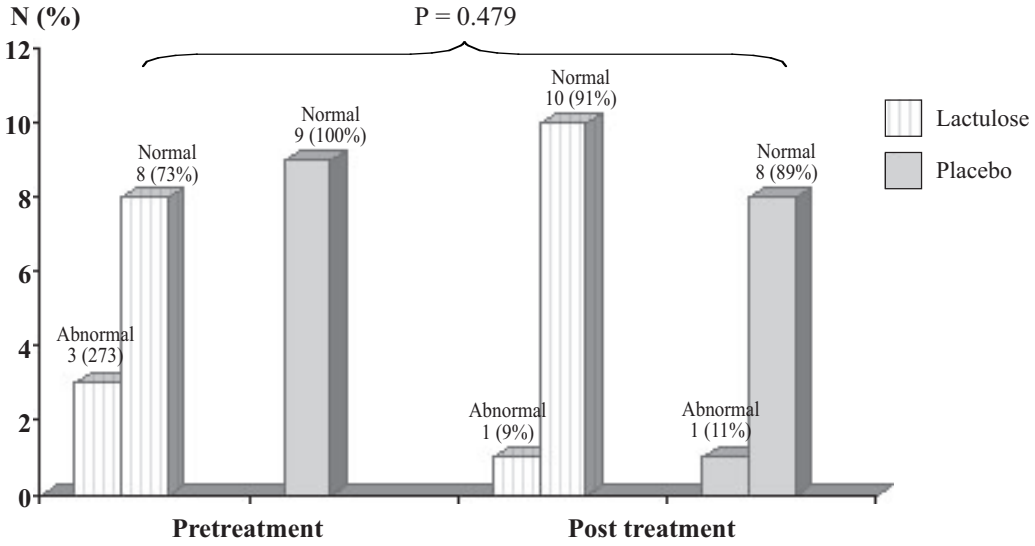

Figure 2 Comparative effect of lactulose and placebo on EEG patterns

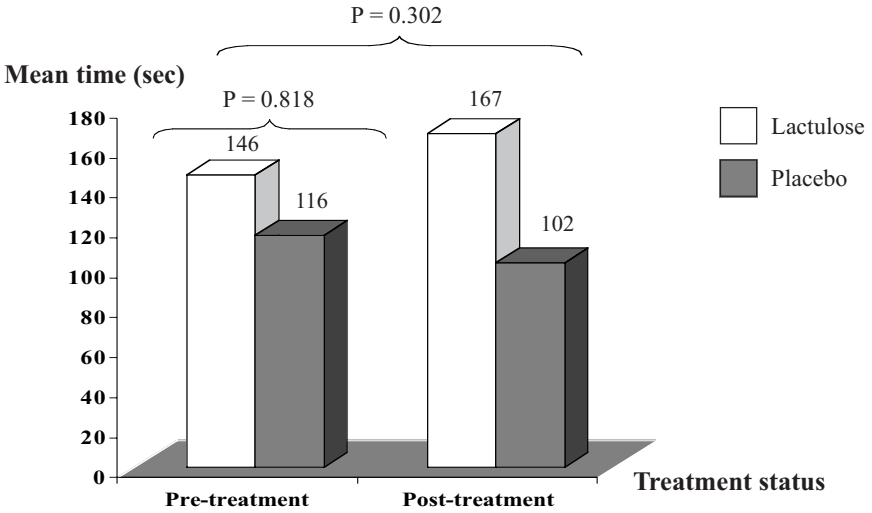

Figure 3 Mean time used in NCT when compared pre and post treatment in both groups

showed abnormal in 1 patient in the lactulose group and 1 patient in placebo group (P = 0.479). (Figure 2)

Mean time used in NCT pre and post treatment in the lactulose group was 145.9 ± 75.9 sec and 167 ± 164.8 sec, as compared to 115.7 ± 71.8 sec and 102.4 ± 65.5 sec in the placebo group. No significant improvement in time used for NCT was found between both groups at the end of treatment. (P = 0.302) (Figure 3)

Psychometric tests

For BDT and DST, we categorized the test result of each patient in both groups into 3 groups from Z-score including the normal group with Z score < -1 SD, mild impairment with -1 SD ≤ Z-score < -2 SD and moderate to severe impairment with Z-score ≥ -2 SD

Improvement after treatment was determined by improvement of Z-score from moderate-severe impairment to mild impairment or to normal and also mild impairment to normal.

On the contrary, worsen outcome after treatment is defined as the deterioration of Z score from normal to mild impairment or moderate-severe impairment and also from mild impairment to mod-severe impairment.

For BDT, there was no patients in normal group, 8 patients in mild impairment group and 3 patients in moderate-severe impairment from lactulose group and

there was 1 patient in normal group, 4 patients in mild impairment group and 4 patients in moderate-severe impairment group from placebo group.

At the end of treatment, there were 11 and 7 patients in mild impairment from lactulose and placebo group, respectively. There were 2 patients in moderate-severe impairment from placebo group and no patient in normal group from both lactulose group and placebo group. (Table 2)

Improvement of BDT test was seen in moderate-severe impairment from lactulose group. For placebo group, there was improvement in moderate-severe impairment but worsen of the test was also seen in normal group (P = 0.189).

For DST, there were 7 patients in mild impairment and 4 patients in moderate-severe from lactulose group. 8 patients in mild impairment and 1 patient in moderate-severe from placebo group were observed in the pretreatment period. After completion of the study, 9 patients and 2 patients were detected in mild impairment and moderate-severe impairment from lactulose group.

In placebo group, there were 1 patient in normal, 7 patients in mild impairment and 1 in moderate-severe impairment (Table 3).

Improvement of DST test was seen in both mild impairment and moderate-severe impairment from lactulose group. In placebo group, improvement was seen in mild impairment but not for moderate to severe impairment (P = 0.770).

DISCUSSION

The prevalence of SHE has been reported to vary between 30-70% in cirrhotic patients.[13-18] This variation in prevalence is due to differences in diagnostic methods, patients studied, and definitions of SHE used in the different studies. We defined SHE as the presence of at least two abnormal psychometric tests or abnormal slowing of EEG. By using this definition, we found that the prevalence of SHE was 27.3% in our outpatient cirrhotic population

There is increasing evidence to show that SHE is an important disorder that could seriously impaired daily living and health related quality of life (HRQOL) in cirrhotic patients. Several studies using unabsorbable saccharides, dietary manipulation, and branched chain amino acid have shown some improvement in SHE after treatment.[23-26] Similar to the pathogenesis of HE, SHE should be considered receiving treatment with lactulose.[20] Lactulose has an established role in the management of patient with overt HE for many years.

Table 2 Comparison Pre and Post treatment in both groups in BDT test

Block Design Test	Pre treatment		P-value	Post treatment		P-value
	Lactulose N (%)	Placebo N (%)		Lactulose N (%)	Placebo N (%)	
Normal	0 (0%)	1 (11.1%)	P = 0.362	0 (0%)	0 (0%)	P = 0.189
Mild impairment	8 (72.7%)	4 (44.4%)		11 (100%)	7 (77.8%)	
Moderate-severe impairment	3 (27.3%)	4 (44.4%)		0 (0%)	2 (22.2%)	
Total	**11 (100%)**	**9 (100%)**		**11 (100%)**	**9 (100%)**	

Table 3 Comparison Pre and Post treatment in both groups in DST test

Digit Symbol Test	Pre treatment		P-value	Post treatment		P-value
	Lactulose N (%)	Placebo N (%)		Lactulose N (%)	Placebo N (%)	
Normal	0 (0%)	0 (0%)	P = 0.319	0 (0%)	1 (11.1%)	P = 0.770
Mild impairment	7 (63.6%)	8 (88.9%)		9 (81.8%)	7 (77.8%)	
Moderate-severe impairment	4 (36.4%)	1 (11.1%)		2 (18.2%)	1 (11.1%)	
Total	**11 (100%)**	**9 (100%)**		**11 (100%)**	**9 (100%)**	

The impact of treatment with lactulose on natural history of SHE is unknown.

We performed a study to determine the efficacy of lactulose in cirrhotic patients with SHE. At the end of treatment, 2 months, we found that the time needed to complete NCT did not significantly improve after lactulose treatment when compared with placebo.

From this study, we concluded that there was a trend for efficacy of lactulose in the treatment of cirrhotic patients with SHE, even though there was no significantly different improvement in both psychometric and neurophysiological tests between lactulose and placebo group, which could be due to the small number of patients. Therefore, more patients are need to be gathered in a future study to document the efficacy of lactulose for treatment of SHE.

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