The Effect of Domperidone on Intestinal Motility and Bacterial Overgrowth in Patients with Liver Cirrhosis

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ABSTRACT

Background: *Spontaneous bacterial peritonitis (SBP) is a common serious complication of liver cirrhosis mainly caused by bacterial translocation (BT) into ascites fluid. The most essential issue that affects BT is small intestinal bacterial overgrowth (SIBO), which usually caused by gastrointestinal dysmotility. This study was aimed to evaluate the prokinetic effects of domperidone on gastrointestinal motility and small intestinal bacterial overgrowth and the correlation between restoration of motility and the incidence of SIBO in patients with liver cirrhosis.*

Method: *A cross-over double blind clinical trial was conducted on patients who were treated at the ward and outpatient clinic from Division of Hepatology in Cipto Mangunkusumo Hospital, Jakarta and Soedarso Hospital, Pontianak between September 2010 and March 2011. All patients suffered from liver cirrhosis with ascites, gastrointestinal dysmotility and SIBO were included in the study. Out of 34 eligible patients, 16 patients received placebo and 18 patients received prokinetics (domperidone). Wilcoxon test was performed to analyze the comparison of SIBO before and after treatment in the placebo group; while paired T-test was employed for the prokinetics (domperidone) group. To evaluate improved balance of SIBO in the placebo and domperidone group, a Chi-square test was performed.*

Results: *In the placebo group, 61.8% patients experienced SIBO; while in the prokinetics group, SIBO occurred only in 2.9% patients. Restored gastrointestinal motility took place in the prokinetics group with reduced median value for orocaecal transit time from 120 minutes into 90 minutes ($p = 0.0001$). In contrast, it went worse in the placebo group, i.e. from 90 minutes into 110 minutes ($p = 0.002$). There was a significant correlation between restored gastrointestinal motility and SIBO ($p = 0.0001$). Similarly, so does the effect of administering prokinetic agent on restored gastrointestinal motility ($p = 0.0001$) and SIBO ($p = 0.0001$).*

Conclusion: *The administration of prokinetics has been proven effective to restore gastrointestinal motility that may lead to reduced incidence of SIBO in patients with liver cirrhosis.*

Keywords*: prokinetics, breath hydrogen test, dysmotilitas, bacterial overgrowth*

ABSTRAK

Latar belakang: *Peritonitis bakteri spontan (PBS) merupakan komplikasi yang sering dan fatal pada sirosis hati. Penyebabnya utamanya adalah translokasi bakteri (TB) ke dalam cairan asites. Hal yang paling berperan dalam TB adalah adanya tumbuh lebih bakteri intestinal (TLB) yang biasanya disebabkan gangguan motilitas. Penelitian ini bertujuan untuk melihat pengaruh prokinetik domperidon terhadap motilitas dan TLB intestinal serta hubungan antara perbaikan motilitas dengan kejadian TLB pada pasien sirosis.*

Metode: *Dilakukan uji klinik tersamar ganda bersilang pada pasien di bangsal rawat inap dan poliklinik Divisi Hepatologi Rumah Sakit Cipto Mangunkusumo, Jakarta dan Rumah Sakit Soedarso, Pontianak pada September 2010 hingga Maret 2011. Semua pasien penderita sirosis hati dengan asites yang mengalami gangguan motilitas dan TLB diikutsertakan. Dari 34 pasien yang memenuhi kriteria, sebanyak 16 pasien diberi plasebo dan 18 pasien diberi prokinetik (domperidon). Digunakan uji Wilcoxon untuk menganalisis perbandingan TLB sebelum dan sesudah perlakuan pada kelompok plasebo dan uji-T berpasangan untuk kelompok prokinetik domperidon. Untuk melihat perbaikan TLB pada kelompok plasebo dan domperidon digunakan uji Chi-square.*

Hasil: *Pada kelompok plasebo 61,8% pasien mengalami TLB, sedangkan pada kelompok prokinetik, TLB hanya terjadi pada 2,9% pasien. Perbaikan motilitas terjadi pada kelompok prokinetik dimana median waktu transit oroseikal berkurang dari 120 menit menjadi 90 menit (p = 0.0001). Sedangkan pada kelompok plasebo justru memburuk dari 90 menit menjadi 110 menit (p = 0,002). Terdapat hubungan bermakna antara perbaikan motilitas dengan TLB intestinal (p = 0,0001). Begitu pula dengan pemberian prokinetik terhadap perbaikan motilitas (p = 0,0001) dan TLB intestinal (p = 0,0001).*

Simpulan: *Pemberian prokinetik terbukti dapat memperbaiki motilitas sehingga dapat menurunkan kejadian TLB intestinal pada pasien sirosis hati.*

Kata kunci*: prokinetik, breath hydrogen test, dismotilitas, tumbuh lebih bakteri*

INTRODUCTION

Liver cirrhosis is one of hepatologic problems which has a relatively high morbidity and mortality. Among major complications of liver cirrhosis, the most common one is ascites.

Liver cirrhotic patients with ascites have greater vulnerability for bacterial infection. Among them, the most common and fatal complication (25%) is spontaneous bacterial peritonitis (SBP).[1-3] When it was first diagnosed in 1970, the prevalence only reached 5-10% in patients with liver cirrhosis who also had ascites. In conjuction with advances in diagnostic approaches, several recent studies demonstrated that it occurs in 10-30% liver cirrhotic patients who also had ascites.[4,5] The mortality has been reduced from 80% - 100% in 1970's era into 20-40% nowadays. However, certain condition such as renal damage that usually go together with SBP still has great contribution for high mortality rate which may be as high as 100%.[2,4-6] Moreover, there is no national data in Indonesia about the prevalence of liver cirrhosis; however, clinical data on patients with liver cirrhosis who have been hospitalized at internal medicine wards ranges about 3.6 – 8.4%.[7]

Some studies suggested that SBP in liver cirrhotic patients with ascites is a result of small intestinal bacterial translocation (SIBO), which has been transferred to extra-intestinal region, including into ascites fluid. As it is widely known, there is an existence of increased adrenergic tone in liver cirrhosis, which leads to reduced intestinal motility. The hypomotility condition causes longer intestinal transit time. It favors a chance for developing small intestinal bacterial overgrowth (SIBO). In addition, structural and functional damage of intestinal mucosal barrier against infection and suppressed immune system in patients with liver cirrhosis will further facilitate bacterial translocation and its products to extra-intestinal region, including into ascites fluid.[1-5,8-10] Advances in diagnostic and therapeutic technologies have caused shifting paradigm of SBP from a deadly complication into something that can be managed and prevented. Various efforts have been proposed to complete or support treatment for SBP in order to have better outcomes. One of them includes improving gastrointestinal motility using prokinetic agents. Several studies recommended that administration of prokinetics as a supplementation of antibiotic treatment may reduce SBP morbidity and mortality.[1,11-15] Of some prokinetic agents available in Indonesia, the relatively safe agent is domperidone. However, there is no empirical evidences in Indonesia, which reveal the effectiveness of domperidone in restoring intestinal motility to prevent or reduce bacterial overgrowth in cirrhotic patients with ascites.

METHOD

This study was a cross-over double blinded clinical trial, which was conducted in 34 liver cirrhotic patients with ascites who visited outpatient clinic and ward of Hepatology Division in Cipto Mangunkusumo Hospital and Soedarso Hospital located in Pontianak, West Kalimantan between September 2010 and March 2011. All patients with liver cirrhosis and ascites

aged 16 years or more (≥ 16 years) who also had gastrointestinal dysmotility and intestinal bacterial overgrowth received information about the objectives, advantages and risks of the study. Those patients were included in the study after they signed informed consent forms. Patients who could not sign informed consent form or who had other conditions that may affect study results were excluded from the study, including those with active pulmonary tuberculosis, disseminated intravascular coagulopathy, urinary tract infection, tuberculosis peritonitis, other abdominal wall infections, heart failure, hepatorenal syndrome, active bleeding and fever of more than 38°C.

Slowed gastrointestinal motility is a gastrointestinal movement which is slower than normal (normal limit 70-90 minutes); while restored motility is an improved response of motility and characterized by faster orocaecal transit time after treatment compared to before treatment. Furthermore, an orocaecal transit time is the time needed by a substrate, lactulose, after being ingested until it reaches caecum. Longer or slower transit time is characterized by increased H_2 of or more than 10 ppm compared to the basal H_2 concentration starting from the 60 minutes during breath hydrogen test (BHT).

Eligible subjects who fulfilled the inclusion criteria were assessed with baseline screening including taking medical history, performing physical examination and laboratory tests. Data of examination and test results was recorded in a questionnaire form. Subjects were then randomly categorized into two groups. The first group was 16 subjects who received placebo; while the second group included 18 subjects who received prokinetics, i.e. domperidone. After 10 days, BHT was performed again to evaluate intestinal bacterial overgrowth and intestinal motility. Both groups received a phase of free wash-out period for 1 week. Subsequently, the first group received prokinetics and the second group received placebo for 10 days. BHT evaluation was repeated after the treatment had been completed.

Data obtained from questionnaires was entered to data tables using computer program of SPSS. Data normality was tested using Kolmogorov Smirnov test. To analyze the comparison of SIBO on BHT between before and after treatment, Wilcoxon test was performed in the placebo group since the data was not normally distributed. While paired T-test was performed to analyse the comparison of SIBO on BHT before and after treatment in the domperidone group as the data was normally distributed. To evaluate improved SIBO in placebo and domperidone group, a table of 2 x 2 was used and it was further evaluated using Chi-square test.

RESULTS

Of 34 subjects, there were 23 (67.6%) male subjects. Mean age was 53.8 ± 9.1 years. BMI of both groups, placebo and prokinetics groups, was not significantly different. Mean value of hemoglobin level, platelet counts, blood glucose level, prothrombin time, albumin level, aspartat transaminase (AST), alanin aminotransferase (ALT) level as well as median value of leukocytes count between placebo group and prokinetics groups were not significantly different. Child-Pugh class B was mostly found in both groups; however, there was no significant difference on criteria A, B, and C (Table 1).

Figure 1 shows that there was greater bacterial overgrowth in placebo group (61.8%) compared to prokinetics group (2.9%). Whereas the results of orocaecal transit time (OCTT) before and after treatment in placebo group revealed that the median value before treatment was 90 (90-110) minutes; while after treatment, the median value was 110 (90-110) minutes. In the prokinetics group, the median value before treatment was 120 (90-120) minutes, while after treatment the median of OCTT results was 90 (60-120) minutes. It indicates that the OCTT in placebo group before and after treatment had worse results ($p = 0.002$); while in prokinetics group, there were better results ($p = 0.0001$).

A significant correlation was found between improved OCTT and better value of SIBO, which suggests that the greater OCTT improvement, the better value of restored SIBO ($p = 0.0001$) (Table 2). Restored SIBO and improved OCTT also showed significant correlation, both in placebo and prokinetics groups (Table 3).

DISCUSSION

We found that there was a greater bacterial overgrowth in placebo group (61.8%) compared to prokinetics group (2.9%). Moreover, for OCTT in placebo group before and after treatment, there was worse result ($p = 0.002$); in contrast, in prokinetics group, we found better result ($p = 0.0001$). This finding is consistent with several studies revealing the benefits of prokinetics supplementation to restore gastrointestinal motility and to reduce SIBO incidence

Table 1. Characteristics and comparison of laboratory test results between placebo and prokinetics group

Variable	Subjects (n = 34)	Placebo (n = 16)	Domperidon (n = 18)	p
Sex				
Male	23 (67.6%)	11 (68.8%)	12 (66.7%)	1.000*
Female	11 (32.4%)	5 (31.3%)	6 (33.3%)	
Age (years)#	53.85 ± 9.1	54.94 ± 9.08	52.89 ± 9.34	0.783**
< 40	2 (5.9%)	0	2 (11.1%)	0.400*
40-50	12 (35.3%)	6 (37.5%)	6 (33.3%)	0.738*
50-60	14 (41.2%)	7 (43.8%)	7 (38.9%)	1.000*
> 60	6 (17.6%)	3 (18.8%)	3 (16.7%)	1.000*
Education				
Elementary school	10 (29.4%)	3 (18.8%)	7 (38.9%)	1.000
Junior high school	12 (35.3%)	7 (43.8%)	5 (27.8%)	
Senior high school	11 (32.4%)	5 (31.3%)	6 (33.3%)	
College	1 (2.9%)	1 (6.3%)	0	
BMI (kg/m^2)	23.67 ± 2.85	23.23 ± 2.04	24.07 ± 3.46	0.204**
Hemoglobin (g/dL)		10.18 ± 0.99	10.84 ± 1.73	0.191**
Thrombocytes (cell/mL)		90,937.5 ± 41,746	114.666.7 ± 46.599.6	0.13**
Random blood glucose level (mg/dL)		106 ± 16.18	109.2 ± 15.47	0.590**
Albumin (g/dL)		2.71 ± 0.41	2.81 ± 0.7	0.639**
AST (u/L)		82.03 ± 57.2	56.06 ± 19.73	0.079**
ALT (u/L)		58.37 ± 24	40.87 ± 13	0.110**
Prothrombin time (second)		15.51 ± 1.45	15.04 ± 1.57	0.369**
Leukocyte (cell/mL)		6731.25 ± 5517.1	12208.8 ± 23021.7	0.67***
Child-Pugh				
A		1 (6.3%)	3 (16.7%)	1.000*
B		8 (50%)	9 (50%)	
C		7 (43.8%)	6 (33.3%)	

*Chi-square test; **independent T-test; ***Mann-whitney test; #(mean, SD); BMI: body mass index; AST: aspartate transaminase; ALT: alanin aminotransferase

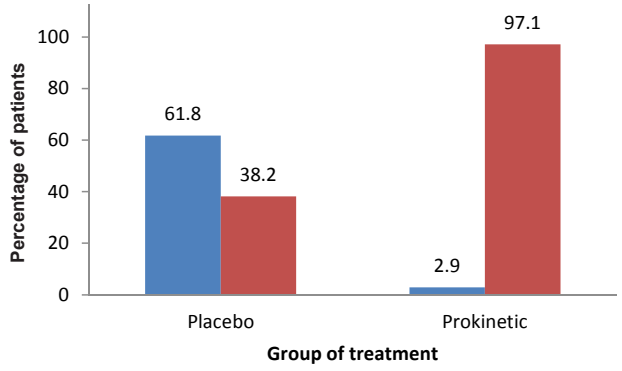

Figure 1. Bacterial overgrowth in placebo and prokinetics group

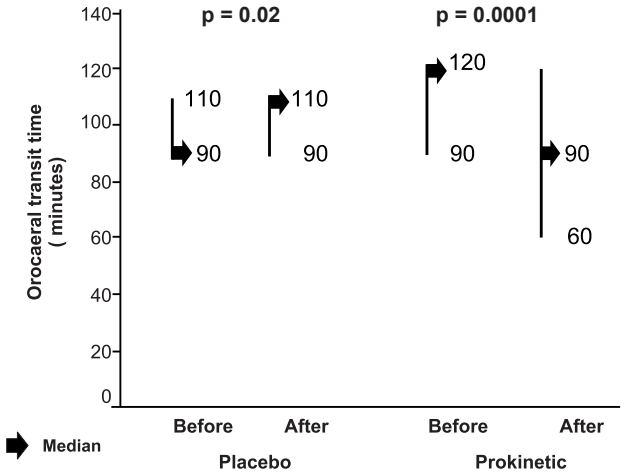

Figure 2. Orocaecal transit time in placebo and prokinetics group

Table 2. Correlation between improved orocaecal transit time and restored SIBO

OCTT	SIBO value		p*
	Restored	Not restored	
Improved	18 (100%)	0 (0%)	0.0001
Not improved	28 (56%)	22 (44%)	

*Chi-square test; OCCT: orocaecal transit time; SIBO: small intestinal bacterial translocation

Table 3. Correlation of restored SIBO and motility between placebo and prokinetics groups

	Randomization		p*
	Placebo	Prokinetic	
SIBO score			
Improved	13 (38.2%)	33 (97.1%)	0.0001
Not improved	21 (61.8%)	1 (2.9%)	
OCCT			
Improved	0 (0%)	18 (52.9%)	0.0001
Not improved	34 (100%)	16 (47.1%)	

*Chi-square test; SIBO: small intestinal bacteria translocation; OCCT: orocaecal transit time

that may prevent the development of SBP.[13] Several experimental studies conducted by Shun-Chai Zang et al and Pardo et al in male rats with liver cirrhosis which also had bacterial overgrowth and hypomotility showed that prokinetics supplementation (cisapride) may reduce SIBO incidence and lower intestinal transit time. Shun-Chai Zang revealed that the incidence of SIBO in male rates receiving prokinetics was lower compared to placebo group (15% vs. 80%, $p < 0.01$). Moreover, rats that received prokinetics also experienced improved intestinal transit time compared to placebo group.[16,17]

In liver cirrhosis, there is increased adrenergic tone which results in reduced intestinal motility. Hypomotility condition causes longer intestinal transit time. It favors a chance for developing SIBO. In addition, structural and functional damage of intestinal mucosal barrier against infection and immunocompromised condition experienced by patients with liver cirrhosis facilitate bacterial translocation and its products to extra-intestinal region, including into ascites fluid.[1-5,8-10] Gupta et al reported a correlation between bacterial overgrowth and slower orocaecal transit time, which affects SIBO incidence in patients with liver cirrhosis of child B and C criteria by 69.2%.[9] Several previous studies have even revealed that prevention of SIBO extremely depends on the normality of intestinal motility.[18-21] It is supported by some findings that there was hypomotility in experimental animals with cirrhosis, which also experienced SIBO and lower SIBO incidence in animals with hypomotility that treated with prokinetics agents.[16,17] Based on the pathogenesis, theoretically, improved intestinal transit time/OCTT will improve the incidence of SIBO. In this study, we found a significant correlation between improved OCTT and improved SIBO, which indicated that the greater improvement of OCTT, the better value of improved SIBO ($p = 0.0001$) (Table 2). Such finding is consistent with the results of study conducted by Simadibrata, which reported a statistically significant correlation between gastrointestinal motility expressed in OCTT and the development of SIBO ($p = 0.008$).[22] A study conducted by Gupta et al has found a correlation between dysmotility and SIBO in patients with liver cirrhosis.[9]

With regard to the correlation between placebo or prokinetics and bacterial overgrowth as well as the restored motility, this study has also found significant results. Some other studies have also revealed similar results although using different materials and methods. For example, a study conducted by Tatsuta et al compared the supplementation of cisapride on placebo and cisapride on domperidone. The study was a cross-over double blinded clinical trial in patients who had delayed gastric emptying. Obviously, in the group with cisapride and domperidone, they found improved gastric emptying time, which was statistically significant compared to the group receiving cisapride and placebo ($p < 0.005$).[23]

CONCLUSION

Prokinetics can restore intestinal motility in patients with liver cirrhosis who experience some disorders and may reduce the incidence of SIBO.

SUGGESTION

Further studies should be conducted, particularly comparison between restored intestinal motility and bacterial overgrowth in patients with liver cirrhosis by comparing improvement in liver function paramaters using more sensitive and higher specificity methods.

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