ABSTRACT

Introduction: Spontaneous bacterial peritonitis (SBP) is one of the most serious complications in cirrhotic patients. It has been reported that acid suppressants such as PPIs or H2RAs might cause small intestine bacterial overgrowth and bacterial translocation. However, little information is available whether acid suppression increases the risk of SBP and affects mortality rate in patients with advanced cirrhosis. Therefore, we designed a multi-center, cohort study that included a large number of cirrhotic patients to evaluate whether acid suppressive therapy increases the risk of SBP and to define the factors associated with mortality after SBP in cirrhotic patients with ascites.

Methods: Cirrhotic patients who had undergone paracentesis after hospitalization were included. Those patients were divided into two groups according to the presence or absence of SBP. Factors associated with the development of SBP were analyzed. Mortality rates during hospitalization or within 30 days after SBP and the factors associated with mortality were also

analyzed.

Results: A total of 1140 patients [Median age, 62; Men, 75%; model for end-stage liver disease (MELD) score, 17] were included. Five hundred thirty three patients were identified as having SBP. In the logistic regression, the use of histamine-2 receptor antagonists (H2RAs), the use of proton pump inhibitors (PPIs), a high admission MELD score, and old age were associated with the development of SBP. The use of PPIs within 30 days (adjusted odds ratio [aOR], 1.960; 95% confidence interval [CI], 1.190 to 3.227; P=0.008), a higher admission MELD score (aOR, 1.054; 95% CI, 1.032 to 1.076; P<0.001), and hepatocellular carcinoma (aOR, 1.852; 95% CI, 1.256 to 2.730; P=0.002) were associated with mortality after SBP.

Conclusions: Acid suppressive therapy is associated with the development of SBP in cirrhotic patients with ascites. The use of PPIs is associated with mortality after SBP independent of the severity of the underlying liver disease in our retrospective cohort study.

Keywords: Cirrhosis, Proton pump inhibitors, Histamine-2 receptor antagonists, Peritonitis, Mortality

Student number: 2012-22679

CONTENTS

LIST OF TABLES AND FIGURES

INTRODUCTION

Spontaneous bacterial peritonitis (SBP) is one of the most serious complications in cirrhotic patients, which is associated with the increased morbidity and mortality(1). Although the precise mechanism by which SBP develops in cirrhotic patients is unclear, intestinal bacterial overgrowth resulting from delayed intestinal motility plays a critical role as well as increased intestinal permeability, a low level of immunoglobulin or complement proteins, and down-regulated phagocytic functions(2-4).

Acid suppressants such as proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) have been widely prescribed for patients with peptic ulcer disease, gastroesophageal reflux disease (GERD), and non-ulcer dyspepsia (NUD) because they are generally safe and efficacious(5). Acid suppressants exert their effects by reducing gastric acid in the stomach(6). However, gastric acid secretion physiologically has a critical role in defense against various enteric pathogens by decontaminating the stomach and proximal small intestine(7). Therefore, alteration in gastric pH

by administration of acid suppressants can change the normal gastrointestinal flora, leading to decreased elimination of pathogenic colonization and increased risk of infection such as pneumonia in critically-ill patients and enterocolitis caused by *Clostridium difficile* and *Salmonella* species(8,9).

The epidemiologic evidence for an association between the use of acid suppressants and the development of SBP has been studied. It has been reported that acid suppressants are associated with an increased risk for the development of SBP in cirrhotic patients(10,11). In a recent meta-analysis, there was a significant association between the use of PPIs and the development of SBP(12). Although these studies provide evidence for an association between the use of acid suppressants and the development of SBP, controversial results have reported in recent studies(13,14). In addition, most of these studies include a relative small number of patients. More importantly, it remains unclear that acid suppressive therapy in patients with cirrhosis is associated with mortality independent of the severity of the underlying liver function. Therefore, we designed a multi-center, cohort study that included a large number of cirrhotic patients to evaluate whether acid

suppressive therapy increases the risk of SBP and to define the factors associated with mortality after SBP in cirrhotic patients with ascites.

MATERIALS AND METHODS

1. Patients

The study protocol was approved by the Institutional Review Board of Seoul National University Hospital and Seoul National University Boramae Medical Center. A total of 1437 consecutive cirrhotic patients with ascites who had undergone diagnostic paracentesis after admission to Seoul National University Hospital or Seoul National University Boramae Medical Center from January 2003 to December 2010 were included in this study. Liver cirrhosis was established by liver biopsy or by clinical evidence of cirrhosis such as varices or radiologic evidence in ultrasonogram, computed tomography (CT), and magnetic resonance imaging (MRI) in patients with chronic liver disease. Diagnostic paracentesis was performed on most of the cirrhotic patients with ascites that were admitted to the two medical centers, regardless of the reason for hospitalization. The exclusion criteria for the cases included gastrointestinal bleeding within the preceding 14 days prior to admission (n=8), organ transplantation (n=177), unclear medical record or antibiotic use within 2 weeks prior to

admission (n=74), the inability to have medication list on admission (n=3), tuberculous peritonitis (n=1) or carcinomatosis (n=1) or HIV (n=1). Gastrointestinal bleeding was defined as evidence of melena or hematochezia, or a drop in hemoglobin of 2g/dl or more from the previous result, or the need for a transfusion. Consequently, the remaining 1140 patients were eligible for the analysis.

2. Methods

Clinical and follow-up data were obtained by reviewing the electric medical recording system. Those patients were divided into two groups according to the presence or absence of SBP. SBP was defined as ascitic fluid polymorphonuclear (PMN) cells $\geq 250mm^3$ with/without a positive fluid culture. Data collected included age, gender, etiology of cirrhosis, history of variceal bleeding or hepatic encephalopathy, Child-Pugh class, model for end-stage liver disease (MELD) scores, and a history of PPIs or H2RAs use. The high MELD score was defined as score equal or greater than 25 at admission(15). The indications and duration of acid suppressants prior to admission were also reviewed. The results of the laboratory

tests at admission were also reviewed including total bilirubin, albumin, creatinine, and prothrombin time. The number of PMN neutrophils, the protein level, and the culture results of the ascitic fluid were also obtained.

It has been demonstrated that PPIs use 48 hours after initial dose induces increasing and sustained gastric acid suppressio n(16). In addition, a single use of PPIs in a day may cause protopathic bias. Based on these evidences, the use of acid s uppressants was defined as the use of any PPIs or H2RAs a t least for more than 2 days. The use of acid suppressants was defined as the use of any PPIs or H2RAs at least for more than 2 days. Because therapeutic doses of PPIs or H2RAs reach a steady state after daily dosing and thus achieve their maximal effective level between 5 to 7 days(16,17) and a previous study did not show an association with PPIs use in the previous 90 days but not within the previous 7 days(11), we classified the use of acid suppressants as follows: the use of acid suppressants within the previous 7 days, within the previous 4 weeks but not within the past 7 days, and no use of acid suppressants. In the case of repeated SBP, the first event was included in the analysis. To evaluate the appropriate use of acid

suppressants, we define the appropriate indications as follows: GERD, peptic ulcer disease, Barrett's esophagus, Zollinger-Ellison syndrome, and non-steroidal anti-inflammatory drug use. To investigate the mortality rate during hospitalization or within 30 days after the index SBP and predictive factors associated with mortality after SBP, follow-up data were obtained by reviewing the electronic medical recording system.

3. Statistical analysis

Patients who had SBP after paracentesis were compared with those without SBP. Univariable analyses were performed using the Student's *t*-test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. The binary logistic regression analysis was performed using a forward stepwise selection method. To investigate the mortality rate and SBP-related mortality factors, patients who died during hospitalization or within 30 days after the index SBP were compared with those who survived > 30 days after SBP. Multivariate analysis was done with the binary logistic regression. Statistical significance was determined using a *P*-value < 0.05. All analyses were carried out using SPSS for

Windows version 19.0 (IBM, New York, USA).

RESULTS

A total of 1140 consecutive patients were included in the analysis. Of those, 533 patients were confirmed to have SBP through paracentesis. The demographic and clinical details of the two groups are summarized in Table 1.There were no significant differences in age and gender between the two groups. There was a significant difference in the etiology of the chronic liver disease. Of those, chronic hepatitis B was the most common cause of cirrhosis in both two groups. In the SBP group, patients had a higher proportion of Child-Pugh class C, a higher rate of PPIs or H2RAs use, and higher rates of a previous history of hepatic encephalopathy.

Details of acid suppressive therapy were analyzed. Among the patients with SBP, 127 patients were treated with PPIs or H2RAs. Pantoprazole was the PPI most frequently used in both group. Indications of acid suppressive therapy included GERD (28.3%), peptic ulcer disease (2.4%), Barrett's esophagus (1.6%), and esophageal varix bleeding or portal hypertensive gastropathy (48.0%). Twenty-six patients (19.7%) had no

documented indication. Of the patients with acid suppressants, 67.7% in 127 patients with SBP had inappropriate indication of acid suppressive therapy. A significant difference in the indication of acid suppressive therapy was not found between the two groups.

Table 1. Demographic, clinical, and laboratory characteristics of patients with or without spontaneous bacterial peritonitis

Variables	SBP (n=533)	No SBP (n=607)	*p* value
Age (years)	62.7±9.5	62.0±10.4	0.166
Gender (M/F)	410/123	449/158	0.248
Causes of cirrhosis			0.011
HBV (%)	402 (75.4)	433 (71.3)	
HCV (%)	62 (11.6)	76 (12.5)	
Alcohol (%)	43 (8.1)	37 (6.1)	
Others (%)	26 (4.9)	61 (10.0)	
Use of beta blocker (%)	62 (11.6%)	71 (11.7%)	0.973
DM (%)	101 (19.0)	136 (22.4)	0.151
HbA1C	6.4±1.0	6.8±5.4	0.097
HCC (%)	286 (53.7)	343 (56.5)	0.414
Causes of admission			0.002
Abdominal distension (%)	125 (23.5)	155 (25.5)	
Development of HCC (%)	25 (4.7)	41 (6.8)	
PSE (%)	60 (11.3)	65 (10.7)	
Diarrhea (%)	1 (0.2)	1 (0.2)	
Abdominal pain (%)	85 (15.9)	48 (7.9)	
Fever (%)	33 (6.2)	24 (4.0)	
TACE (%)	14 (2.6)	21 (3.5)	

Others (%)	190 (35.6)	252 (41.5)	
Child-Pugh class			<0.001
A (%)	3 (0.6)	11 (1.8)	
B (%)	364 (68.3)	478 (78.7)	
C (%)	166 (31.1)	118 (19.4)	
History of EVB (%)	209 (39.2)	207 (34.1)	0.074
History of PSE (%)	100 (18.7)	82 (13.5)	0.016
Ascites PMN (/mm3)	4651.1±15339	26.4±43.5	<0.001
Ascites Protein (g/dL)	1.4±1.0	1.2±0.9	<0.001
Bilirubin (mg/dL)	10.5±11.0	8.9±11.2	0.890
INR	1.9±0.8	1.7±1.0	0.818
Creatinine (mg/dL)	1.8±1.5	1.6±1.4	0.011
Albumin (g/dL)	2.6±0.5	2.7±1.3	0.265
MELD score	19±9.0	16.3±8.5	0.098
PPIs use			<0.001
≤7 days (%)	61 (11.4)	37 (6.1)	
8-30 days (%)	21 (3.9)	10 (1.6)	
H2RAs use			<0.001
≤7 days (%)	35 (6.6)	9 (1.5)	
8-30 days (%)	10 (1.9)	3 (0.5)	

Data presented as mean (SD), unless otherwise stated.

SBP, spontaneous bacterial peritonitis; HBV, hepatitis B virus; HCV, hepatitis C virus; DM, diabetes mellitus; HCC, hepatocellular carcinoma; PSE, porto-systemic encephalopathy; TACE, trans-arterial chemoembolization; EVB,

esophageal variceal bleeding; PMN, polymorphonuclear leukocyte; MELD, model for end-stage liver disease; PPI, proton pump inhibitor; H2RA, histamine receptor type 2 antagonist

Among the 533 SBP patients, bacteriologic confirmation from ascitic fluid was available in 112 patients (21.0%). Escherichia coli was the pathogen most frequently identified and seen in 38 patients. Gram-negative organisms were found in 74 patients and gram-positive organisms were found in 38 patients. Fungus was found in 4 patients (Table 2). Antibiotics-resistant bacteria were found in 9 patients. Of the 9 patients, 5 had methicillin-resistant Staphylococcus or methicillin-resistant coagulase-negative staphylococcus and 4 had extended- spectrum β-lactamase producing bacteria. However, there was no significant difference in the culture positive rates according to the use of acid suppressants (P = 0.054).

PPIs user with SBP showed no significant difference in the rates of gram positive versus gram-negative SBP. In addition, there was no significant difference in isolated microorganisms from SBP patients according to the use of PPIs. There were no significant differences in the rates of drug resistant bacteria in SBP patients with or without PPIs. There were no significant differences in the rates of drug resistant bacteria, sepsis, shock, and intensive care unit admission in patients with SBP with or without acid suppressants.

Table 2. Bacteriologic results in cirrhotic patients with spontaneous bacterial peritonitis

	Ascites culture	Blood culture
Gram negative		
Escherichia coli	38	34
Klebsiella pneumoniae	14	9
Pseudomonas aeruginosa	5	3
Aeromonas hydrophila	4	3
Gram positive		
Streptococcus species	12	8
Staphylococcus species	14	14
Fungus		
Candida species	4	2

Independent predictors of SBP in our cohort were assessed by multivariate logistic regression analysis (Table 3). Risk factors included age (adjusted odds ratio [aOR], 1.015; 95% confidence interval [CI], 1.001 to 1.029; P=0.031) and MELD score (aOR, 1.023; 95% CI, 1.002 to 1.044; P=0.034). PPIs use within the previous 7 days (aOR, 2.095, 95% CI 1.330 to 3.330, P=0.001) and PPIs use within 8 to 30 days of admission (aOR 2.866, 95%CI 1.302 to 6.307, P=0.009) were associated with an increased risk of developing SBP. H2RAs use within 7 days (aOR, 5.998 95% CI, 2.694 to 13.356; P<0.001) and H2RAs use within 8 to 30 days of admission (aOR, 3.835 95% CI, 1.024 to 14.369; P=0.046) were also associated with the development of SBP. We additionally analyzed SBP patients regarding to the use of PPIs.

No significant differences were observed between two groups except for hepatocellular carcinoma and history of esophageal bleeding (Table 4).

Table 3. Multivariate analysis of potential risk factors for the development of spontaneous bacterial peritonitis in cirrhotic patients with ascites

	Odds ratio	95% CI	*p* value
Age	1.015	1.001−1.029	0.031
MELD score	1.023	1.002−1.044	0.034
PPIs use			
≤7 days	2.095	1.330−3.330	0.001
8−30 days	2.866	1.302−6.307	0.009
H2RAs use			
≤7 days	5.998	2.694−13.356	<0.001
8−30 days	3.835	1.024−14.369	0.046

MELD, model for end−stage liver disease; PPI, proton pump inhibitor; H2RA, histamine receptor type 2 antagonist

Table 4. Demographic, clinical, and laboratory characteristics of spontaneous bacterial peritonitis patients with or without proton pump inhibitors

	Use of PPIs (n=82)	No use of PPIs (n=451)	*p* value
Age (years)	61.9±9.9	62.9±9.4	0.361
Gender (M/F)	69/13	341/110	0.091
Causes of cirrhosis			0.371
HBV (%)	67 (81.7)	335 (74.3)	
HCV (%)	8 (9.7)	54 (12.0)	
Alcohol (%)	3 (4.0)	40 (8.9)	
Others (%)	4 (5.0)	22 (4.4)	
Use of beta blocker (%)	6 (7.3)	56 (12.4)	0.185
DM (%)	15 (18.3)	86 (19.1)	0.869
HbA1C	1.1±2.4	1.4±4.1	0.437
HCC (%)	53 (64.6)	233 (51.6)	0.030
Causes of admission			0.787
Abdominal distension (%)	21 (25.6)	104 (23.1)	
Development of HCC (%)	3 (3.7)	22 (4.9)	
PSE (%)	5 (6.0)	55 (12.2)	
Diarrhea (%)	0 (0.0)	1 (0.2)	
Abdominal pain (%)	14 (17.1)	71 (15.8)	

Fever (%)	4 (4.9)	29 (6.4)	
TACE (%)	3 (3.7)	158 (35.0)	
Others (%)	32 (39.0)	11 (2.4)	
Child-Pugh class			0.634
A (%)	0 (0.0)	3 (0.7)	
B (%)	54 (66.0)	310 (68.7)	
C (%)	28 (34.1)	138 (30.6)	
History of EVB (%)	56 (68.3)	153 (34.0)	<0.001
History of PSE (%)	17 (21.0)	83 (18.4)	0.619
Ascites PMN (/mm3)	2663.9±3457.3	5012.42±16587.9	0.202
Ascites Protein (g/dL)	1.4±0.8	1.4±1.1	0.492
Bilirubin (mg/dL)	12.8±11.3	10.1±10.9	0.047
INR	2.0±0.9	1.9±0.8	0.199
Creatinine (mg/dL)	2.1±1.5	1.8±1.6	0.115
Albumin (g/dL)	2.6±0.5	2.6±0.5	0.435
MELD score	20.0±9.7	18.8±8.9	0.262

HBV, hepatitis B virus; HCV, hepatitis C virus; DM, diabetes mellitus; HCC, hepatocellular carcinoma; PSE, porto-systemic encephalopathy; TACE, trans-arterial chemoembolization; EVB, esophageal variceal bleeding; PMN, polymorphonuclear leukocyte; MELD, model for end-stage liver disease; PPI, proton pump inhibitor; H2RA, histamine receptor type 2 antagonist; SBP, spontaneous bacterial peritonitis.

Among 533 patients with SBP, 175 patients (32.8%) died during hospitalization or within 30 days after diagnosis of SBP.

Major causes of death after SBP were hepatic failure (33.8%), hepatocellular carcinoma (21.4%), and sepsis (13.3%). Patients who died within 30 days had a higher proportion of glycosylated hemoglobin (HbA1c), hepatocellular carcinoma, high admission MELD score, and a higher rate of PPIs use. However, there was no significant association in the use of H2RAs between the two groups (Table 5). There was a statistical significant difference in the cumulative mortality rate between SBP patients treated with acid suppressants and those without acid suppressants (91.3% vs. 84.3%, respectively; P =0.048). Using the binary logistic regression, the significant predictors of mortality were the use of PPIs within 30 days (aOR, 1.960; 95% CI, 1.190 to 3.227; P=0.008), a higher admission MELD score (aOR, 1.054; 95% CI, 1.032 to 1.076; P<0.001), and the presence of hepatocellular carcinoma (aOR, 1.852; 95% CI, 1.256 to 2.730; P=0.002) (Table 6).

Table 5. Comparison between spontaneous bacterial peritonitis patients who died or survived during hospitalization or within 30 days after diagnosis

Variables	Died (n=175)	Survived (n=358)	*p* value
Age (years)	62.9±9.0	62.7±9.7	0.767
Gender (M/F)	132/43	278/80	0.567
Causes of cirrhosis			0.936
HBV (%)	135 (77.1)	267 (74.6)	
HCV (%)	19 (10.9)	43 (12.0)	
Alcohol (%)	13 (7.4)	30 (8.4)	
Others (%)	8 (4.6)	18(5.0%)	
Use of beta blocker (%)	22 (12.6%)	40 (11.2%)	0.636
DM (%)	29 (16.6)	72 (20.1)	0.327
HbA1C	8.5±11.0	6.3±1.6	0.007
HCC (%)	110 (62.9)	176 (49.2)	0.003
Causes of admission			0.486
Abdominal distension (%)	42 (24.0)	83 (23.2)	
Development of HCC (%)	10 (5.7)	15 (4.2)	
PSE (%)	21 (12.0)	39 (10.9)	
Diarrhea (%)	0 (0.0)	1 (0.3)	
Abdominal pain (%)	25 (14.3)	60 (16.8)	
Fever (%)	6 (3.4)	27 (7.5)	

TACE (%)	3 (1.7)	11 (3.1)	
Others (%)	68 (38.9)	122 (34.1)	
Child-Pugh class			0.005
A (%)	0 (0.0)	3 (0.8)	
B (%)	105 (60.0)	259 (72.3)	
C (%)	70 (40.0)	96 (26.8)	
Previous history of EVB (%)	60 (34.3)	149 (41.6)	0.103
Previous history of PSE (%)	40 (22.9)	60 (16.8)	0.090
Ascites PMN (/mm3)	3621.9± 9536.2	5154.2± 17479.4	0.192
Ascites Protein (g/dl)	1.5±0.9	1.4±1.2	0.082
Bilirubin (mg/dL)	15.6±13.2	8.1±8.7	<0.001
INR	2.1±1.0	1.8±0.6	<0.001
Creatinine (mg/dL)	2.2±1.7	1.7±1.5	0.003
Albumin (g/dL)	2.7±0.5	2.6±0.5	0.623
MELD score	21.7±10.3	17.6±8.0	<0.001
PPIs use			0.009
≤7 days (%)	29 (16.6)	32 (8.9)	
8-30 days (%)	10 (5.7)	11 (3.1)	
H2RAs use			0.369
≤7 days (%)	15 (8.6)	20 (5.6)	
8-30 days (%)	4 (2.3)	6 (1.7)	

HBV, hepatitis B virus; HCV, hepatitis C virus; DM, diabetes mellitus; HCC, hepatocellular carcinoma; PSE, porto-systemic encephalopathy; TACE, trans-arterial chemoembolization; EVB, esophageal variceal bleeding; PMN, polymorphonuclear leukocyte; MELD, model for end-stage liver disease; PPI, proton pump inhibitor; H2RA, histamine receptor type 2 antagonist; SBP, spontaneous bacterial peritonitis.

Table 6. Multivariate analysis of risk factor for death during hospitalization or within 30 days after SBP in cirrhotic patients

	odds ratio	95% CI	*p* value
Age	1.010	0.987-1.032	0.400
Sex	1.169	0.739-1.848	0.505
MELD score	1.054	1.032-1.076	<0.001
HCC	1.852	1.256-2.730	0.002
PPI use (≤ 30 days)	1.960	1.190-3.227	0.008

MELD, model for end-stage liver disease; PPI, proton pump inhibitor; CI, confidence interval

Because our cohort included patients with HCC, we additionally analyzed factors associated with mortality by excluding patients died from HCC. In the multivariate analysis, old age (aOR, 1.088; 95% CI, 1.056 to 1.121; P<0.001) and use of PPIs within 30 days (aOR, 3.309; 95% CI, 1.228 to 8.922; P=0.018) were significant predictors for morality within 30 days after diagnosis of SBP (Table 7).

Table 7. Risk factor for mortality during hospitalization or within 30 days after SBP in cirrhotic patients by excluding patients died from hepatocellular carcinoma

	odds ratio	95% CI	*p* value
Age	1.088	1.056−1.121	<0.001
PPIs use (≤ 30 days)	3.309	1.228−8.922	0.018

PPI, proton pump inhibitor; CI, confidence interval

DISCUSSION

Recent reports have demonstrated that acid suppressive treatment is associated with increased risk of SBP in cirrhotic patients with ascites(10,18). However, there exist conflicting data in regards to the increased risk of SBP in cirrhotic patients treated with acid suppressants. In a retrospective study, there was no significant difference in the rates of PPIs use in patients with or without SBP(13). In addition, a recent prospective observational study has demonstrated that PPIs use is not an independent factor of bacterial infection including SBP(14). These studies are limited by the data obtained from a single center and a case-control study design, which could enhance the possibility of sample selection bias. Furthermore, most studies did not report the duration of exposure to acid suppressants, which suggest that the positive association could be attributable to protopathic bias. Therefore, we performed a multicenter cohort study, which included a large number of cirrhotic patients who had undergone diagnostic paracentesis designed to investigate the relationship between acid suppressive therapy and the development of SBP and predictive

factors associated with mortality after SBP. In the present study, we demonstrated that acid suppressive therapy is an independent risk factor for the development of SBP as well as higher admission MELD scores and old age in cirrhotic patients with ascites. In addition, our study showed an even stronger association among cirrhotic patients who were treated with acid suppressants within the previous 8 to 30 days of admission, which suggest the causal relationship is not likely to be attributable to protopathic bias. Therefore, we think that this study provided additional information on the relationship between acid suppressive therapy and the development of SBP.

Surprisingly, we also demonstrated that PPIs use, not H2RAs is associated with increased mortality during hospitalization or within 30 days after diagnosis of SBP. In the present study, we first performed a multivariate analysis using our cohort including HCC patients. The multivariate analysis showed that PPIs use, MELD score, and HCC were associated with the SBP-related mortality. However, we think that the effect of HCC progression on mortality in our cohort was significant, which may cause bias. Therefore, we next performed a multivariate analysis after excluding patients who had died of

HCC progression. In this analysis, PPIs use was still an independent risk factor for SBP-related mortality. Therefore, we believe that our data provided additional information regarding SBP-related mortality in patients with LC. To the best of our knowledge, this is the first report to provide evidence for an association of PPIs use and an increased risk of mortality in patients with SBP.

Interestingly, H2RAs was not a significant predictor of mortality even though it is associated with increased risk of SBP. Theoretically, PPI is a more potent acid suppressant and may delay gastric emptying strongly compared with H2RAs(19). PPIs are metabolized in the liver, thereby increasing the risk of toxicity in patients with liver impairment(20). In addition, a previous study has demonstrated that bacterial overgrowth is significantly higher in patients with PPIs compared to H2RAs(21). Furthermore, it has been demonstrated that omeprazole impairs the function of neutrophils by decreasing the production of reactive oxygen, which leads to reduced bactericidal activity(22). However, the precise reasons for the difference between the two acid suppressants on mortality in patients with SBP remain unclear. In addition, our study is

limited by its retrospective design. Therefore, further studies are needed to confirm the result and to elucidate the mechanism including the direct toxic effect of PPIs in cirrhotic patients with SBP.

The prescription of acid suppressants has been rapidly increasing in the past decades(23). In addition, physicians prefer PPIs to H2RAs when a patient complaints of upper gastrointestinal symptoms such as dyspepsia and gastroesophageal reflux because of its higher potency. However, a previous study reported that acid suppressive treatment is unnecessary in 73% of hospitalized patients(24). In addition to this, the use of PPIs was concordant with the indication in only 30% of the cases(25). Moreover, two recent studies reported that the use of PPIs was improperly prescribed in 63% and 39.6% of patients with cirrhosis(26,27). In the present study, two-thirds of the patients receiving PPIs or H2RAs had no established or appropriate indication for acid suppressive treatment. The main reason for acid suppressive therapy use was to prevent gastrointestinal hemorrhage after bleeding from esophageal varix or portal hypertensive gastropathy. However, evidence for a preventive role of acid

suppressants is scarce even for these situations(28). Our study demonstrated that the use of PPIs is an independent risk factor within 30 days after diagnosis of SBP. Also, recent studies demonstrated PPI was associated with an increased risk of infections such as pneumonia and enterocolitis caused by *clostridium difficile, Salmonella,* and *campylobacter*, which may increase mortality in hospitalized cirrhotic patients(29,30). However, the effect of PPIs on GERD, peptic ulcer disease, Barrett's esophagus, Zollinger-Ellison syndrome, and non-steroidal anti-inflammatory drug use has been established in various studies(25,28). Based on these results, clinicians should consider the risk and benefit of PPIs use when prescribing PPIs in LC patients with ascites. In addition, the casual use of either PPIs or H2RAs without demonstrable indications should be restricted in cirrhotic patients with ascites. We think that this study has several strengths compared with previous studies. This was the first multi-center cohort analysis that included the largest number of cirrhotic patients with various underlying chronic liver disease in the literature. Through the design of the study, we were able to deliberately minimize the bias arising from a single center, case-control

study design. In addition, we enrolled a significant proportion of potential cases and investigated a total of 533 cirrhotic patients with SBP, thereby substantially increasing the statistical power compared with previous studies. Furthermore, we carefully excluded the patients that had gastrointestinal hemorrhage or previous antibiotics use and we performed multiple logistic regression analysis using various clinical factors such as the use of beta blocker and HbA1c, thus eliminating confounding factors.

The present study has limitations. Dosage, duration, and metabolism of PPIs would affect the development of SBP and mortality in patients with liver cirrhosis. Moreover, host factors such as race and immunologic factors could be associated with mortality and development of SBP. Unfortunately, we could not investigate potential confounding factors due to lack of medical records and our retrospective study design. In addition, it remains unclear why PPIs use within 8 to 30 day showed a significant result on SBP-related mortality while PPIs use within 7 days did not. A prospective, randomized, placebo-controlled study would provide definitive evidence for an association between acid suppressive therapy and not only the

development of SBP but also an increased risk of mortality after SBP. However, placing these patients under a placebo-controlled randomized trial would be harmful and also unethical because of the higher fatality of SBP in cirrhotic patients with ascites. Therefore, well-designed, prospective cohort studies of cirrhotic patients on acid suppressive therapy, especially for PPIs use can be attempted to properly adjust for potential confounders and to evaluate the appropriate duration or dose of PPIs on various indications in cirrhotic patients with ascites.

In conclusion, acid suppression was associated with the development of SBP in cirrhotic patients with ascites. The use of PPIs was also associated with SBP-related mortality in our retrospective cohort study, which indicates that prescription of PPIs requires the utmost circumspection in cirrhotic patients with ascites. PPIs should be used with appropriate indications considering the risk and benefit in LC patients with ascites.

REFERENCES

1. Ribeiro TC, Chebli JM, Kondo M, Gaburri PD, Chebli LA, Feldner ACA. Spontaneous bacterial peritonitis: How to deal with this life-threatening cirrhosis complication? Therapeutics and clinical risk management. 2008;4(5):919.

2. Runyon BA, Morrissey RL, Hoefs JC, Wyle FA. Opsonic activity of human ascitic fluid: a potentially important protective mechanism against spontaneous bacterial peritonitis. Hepatology. 1985;5(4):634-7.

3. Sánchez E, Such J, Chiva MT, Soriano G, Llovet T, Mercè J, et al. Development of an experimental model of induced bacterial peritonitis in cirrhotic rats with or without ascites. The American journal of gastroenterology. 2007;102(6):1230-6.

4. Rabinovitz M, Kumar S, Kajani M, Van Thiel DH. Role of serum complement, immunoglobulins, and cell-mediated immune system in the pathogenesis of spontaneous bacterial peritonitis (SBP). Digestive diseases and sciences. 1989;34(10):1547-52.

5. Vanderhoff BT, Tahboub RM. Proton pump inhibitors: an

update. American family physician. 2002;66(2):273-80.

6. Huang JQ, Hunt RH. Pharmacological and pharmacodynamic essentials of H(2)-receptor antagonists and proton pump inhibitors for the practising physician. Best Pract Res Clin Gastroenterol. 2001;15(3):355-70.

7. Howden C, Hunt R. Relationship between gastric secretion and infection. Gut. 1987;28(1):96-107.

8. Dial S, Delaney J, Barkun AN, Suissa S. Use of gastric acid suppressive agents and the risk of community-acquired Clostridium difficile associated disease. JAMA: the journal of the American Medical Association. 2005;294(23):2989-95.

9. Laheij RJF, Sturkenboom MCJM, Hassing RJ, Dieleman J, Stricker BHC, Jansen JBMJ. Risk of community-acquired pneumonia and use of gastric acid suppressive drugs. JAMA: the journal of the American Medical Association. 2004;292(16):1955-60.

10. Bajaj JS, Zadvornova Y, Heuman DM, Hafeezullah M, Hoffmann RG, Sanyal AJ, et al. Association of proton pump inhibitor therapy with spontaneous bacterial peritonitis in cirrhotic patients with ascites. The American journal of gastroenterology. 2009;104(5):1130-4.

11. Goel GA, Deshpande A, Lopez R, Hall GS, van Duin D, Carey WD. Increased rate of spontaneous bacterial peritonitis among cirrhotic patients receiving pharmacologic acid suppression. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2012;10(4):422-7.

12. Trikudanathan G, Israel J, Cappa J, O' Sullivan D. Association between proton pump inhibitors and spontaneous bacterial peritonitis in cirrhotic patients a systematic review and meta-analysis. International journal of clinical practice. 2011;65(6):674-8.

13. Campbell MS, Obstein K, Reddy KR, Yang YX. Association between proton pump inhibitor use and spontaneous bacterial peritonitis. Digestive diseases and sciences. 2008;53(2):394-8.

14. van Vlerken LG, Huisman EJ, van Hoek B, Renooij W, de Rooij FW, Siersema PD, et al. Bacterial infections in cirrhosis: role of proton pump inhibitors and intestinal permeability. Eur J Clin Invest. 2012;42(7):760-7.

15. Desai AP, Reau N, Reddy KG, Te HS, Mohanty S, Satoskar R, et al. Persistent spontaneous bacterial peritonitis: a common complication in patients with spontaneous bacterial peritonitis and a high score in the model for end-stage liver disease. Therapeutic advances in gastroenterology. 2012;5(5):275-83.

16. Miner P, Allgood L, Grender J. Comparison of gastric pH with omeprazole magnesium 20.6 mg (Prilosec OTC) om famotidine 10 mg (Pepcid AC) bd and famotidine 20 mg bd over 14 days of treatment. Alimentary pharmacology & therapeutics. 2007;25(1):103-9.

17. Katz P, Ginsberg G, Hoyle P, Sostek M, Monyak J, Silberg D. Relationship between intragastric acid control and healing status in the treatment of moderate to severe erosive oesophagitis. Alimentary pharmacology & therapeutics. 2007;25(5):617-28.

18. Choi EJ, Lee HJ, Kim KO, Lee SH, Eun JR, Jang BI, et al. Association between acid suppressive therapy and spontaneous bacterial peritonitis in cirrhotic patients with ascites. Scandinavian journal of gastroenterology. 2011;46(5):616-20.

19. Sanaka M, Yamamoto T, Kuyama Y. Effects of proton pump inhibitors on gastric emptying: a systematic review. Digestive diseases and sciences. 2010;55(9):2431-40.

20. Thjodleifsson B. Treatment of acid-related diseases in the elderly with emphasis on the use of proton pump inhibitors. Drugs & aging. 2002;19(12):911-27.

21. Thorens J, Froehlich F, Schwizer W, Saraga E, Bille J, Gyr K, et al. Bacterial overgrowth during treatment with omeprazole compared with cimetidine: a prospective randomised double blind study. Gut. 1996;39(1):54-9.

22. Zedtwitz-Liebenstein K, Wenisch C, Patruta S, Parschalk B, Daxböck F, Graninger W. Omeprazole treatment diminishes intra-and extracellular neutrophil reactive oxygen production and bactericidal activity*. Critical care medicine. 2002;30(5):1118-22.

23. Leonard J, Marshall JK, Moayyedi P. Systematic review of the risk of enteric infection in patients taking acid suppression. The American journal of gastroenterology. 2007;102(9):2047-56.

24. Gupta R, Garg P, Kottoor R, Munoz JC, Jamal MM, Lambiase LR, et al. Overuse of acid suppression therapy in hospitalized patients. Southern medical journal. 2010;103(3):207-11.

25. Molloy D, Molloy A, O'Loughlin C, Falconer M, Hennessy M. Inappropriate use of proton pump inhibitors. Irish journal of medical science. 2010;179(1):73-5.

26. Chavez-Tapia NC, Tellez-Avila FI, Garcia-Leiva J, Valdovinos MA. Use and overuse of proton pump inhibitors in cirrhotic patients. Medical science monitor. 2008;14(9).

27. Kalaitzakis E, Björnsson E. Inadequate use of proton-pump inhibitors in patients with liver cirrhosis. European journal of gastroenterology & hepatology. 2008;20(6):512-8.

28. Lodato F, Azzaroli F, Di Girolamo M, Feletti V, Cecinato P, Lisotti A, et al. Proton pump inhibitors in cirrhosis: Tradition or evidence based practice? World journal of gastroenterology: WJG. 2008;14(19):2980.

29. Bajaj JS, Ananthakrishnan AN, Hafeezullah M, Zadvornova Y, Dye A, McGinley EL, et al. Clostridium difficile is associated with poor outcomes in patients with cirrhosis: a

national and tertiary center perspective. The American journal of gastroenterology. 2009;105(1):106-13.

30. Bajaj J, O'Leary J, Reddy K, Wong F, Olson J, Subramanian R, et al. Second infections independently increase mortality in hospitalized cirrhotic patients: The nacseld experience. Hepatology. 2012;56(6):2328-35

국문 초록

서론: 자발 세균 복막염은 간경변 환자에서 발생하는 흔한 합병증 중의 하나이다. 위산억제제의 사용이 장내 세균의 과증식을 유발한다는 보고가 있으나 자발 세균 복막염의 발생과 사망률에 영향을 끼치는 지에 대해서는 연구된 바가 많지 않다. 이에 본 연구에서는 복수를 동반한 간경변 환자에서 위산 억제제의 사용유무가 자발 세균 복막염의 발생 및 사망률에 어떠한 연관성이 있는지에 대해 알아보고자 하였다.

방법: 2003 년부터 2010 년까지 서울대학교병원 및 보라매 병원에서 간경변으로 진단받고 입원 후 복수천자를 시행한 1140 명을 대상으로 자발 세균 복막염 유무에 따라 두 그룹으로 나누어, 자발 세균 복막염의 발생과 복막염 발생 30 일 이내의 사망률에 영향을 끼치는 인자에 대하여 후향적 코호트 분석을 시행하였다.

결과: 간경변을 진단받은 1140 명의 환자 중 533 명이 자발 세균 복막염으로 진단되었으며 위산억제제의 사용, 높은 MELD 점수, 고령이 자발 세균 복막염의 발생과 통계적으로 유의한 연관성이 있었다. 또한 복막염 발생 이후의 사망률은 입원 전 30 일 이내 양성자

펌프 억제제의 사용(p=0.008), 높은 MELD 점수 (p < 0.001), 간암(p=0.002)과 유의한 연관성이 있었다.

결론: 간경변 환자에서 양성자 펌프 억제제의 사용은 자발 세균 복막염의 발생 및 사망률과 유의한 연관성이 있었다. 위산 억제제를 사용시 적절한 적응증을 가진 환자에서 이득과 위험성을 판단하여 투약을 고려해야겠다.

주요어 : 간경변, 양성자 펌프 억제제, 히스타민 수용체 길항제, 복막염, 사망률
학 번 : 2012-22679