Original Article

Proton Pump Inhibitor use Significantly Increases the Risk of Spontaneous Bacterial Peritonitis in Patients with Cirrhosis and Ascites Admitted to a Tertiary Care Hospital in North Odisha

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ABSTRACT

Background: The risk of spontaneous bacterial peritonitis (SBP) associated with proton pump inhibitor (PPI) use has been raised in cirrhotic patients with ascites. However, this is based on case–control studies, often with a small series.

Aim: To determine whether PPI use increases the risk of SBP using a large cohort

Methods: This retrospective cohort study included 1965 cirrhotic patients with ascites diagnosed between March 2020 and August2023. The SBP incidence rate was compared between the PPI and non-PPI groups before and after propensity score matching to reduce the effect of selection bias and potential confounders. Multivariate analysis was conducted to confirm the association of PPI use with SBP.

Results: After excluding 411 patients, 1554 were analysed. Among them, 512 patients (32.9%) were included in the PPI group. The annual SBP incidence rate was higher in the PPI group than in the non-PPI group (10.6% and 5.8%, P = 0.002) before matching. Indications for PPI use and dose of PPI were similar between patients with and without SBP. In the propensity score matched cohort (402 pairs), the SBP incidence rate was also higher in the PPI group than in the non-PPI group (10.8% vs. 6.0%, P = 0.038). Multivariate analysis revealed that PPI use (Hazard ratio 1.396; 95% confidence interval, 1.057–1.843; P = 0.019) was the independent risk factor for SBP.

Conclusion: Proton pump inhibitor use significantly increases the risk of spontaneous bacterial peritonitis in cirrhotic patients with ascites. Proton pump inhibitor use should be undertaken with greater caution and appropriately in patients with cirrhosis.

Keywords: PPI (Proton pump inhibitors), SBP (Spontaneous Bacterial peritonitis), BT (Bacterial Trannslocation), SIBO (mall intestinal Bacterial Overgrowth), CDI (Clostridium Difficile Infection).

INTRODUCTION

Proton pump inhibitors (PPIs) are the most commonly used drugs worldwide.[1] Due to the effect of potent acid suppression, PPIs are effectively used in gastro-oesophageal reflux disease (GERD) and peptic ulcer treatment.[2–6] However, there are growing concerns about the association between PPI use and several potential adverse effects, including enteric infections, pneumonia, bone fractures and cardiovascular risk stemming from its interaction with clopidogrel.[7–10.] Spontaneous bacterial peritonitis (SBP) is the most frequent and life-threatening infection in patients with advanced liver cirrhosis.[11] Bacterial translocation (BT) is the common cause of SBP and transient bacteremia due to invasive procedures could be other source particularly in nosocomial SBP.[11, 12] On the contrary to limited BT to mesenteric lymph node, frequent and/or severe BT may be deleterious.[11] In the development of pathological BT, small intestinal bacterial overgrowth (SIBO), increased intestinal permeability and impaired immunity have been implicated.[13–17] By reducing acid production, PPI therapy may cause SIBO and has been suggested to contribute to an increased risk of SBP.[18–20] However, the association between PPI use and the development of SBP remains controversial with other conflicting results.[21] In addition, the link between PPI use and the development of SBP is based on case–control studies, often in a small series. Thus, these results might be confounded by several factors. The current study sought to determine whether PPI use increases the risk of SBP development in a large cohort composed of cirrhotic patients with ascites, as well was to investigate the characteristics of SBP in PPI user.

METHODS

Study population

This retrospective cohort study included 1965 consecutive liver cirrhosis patients taking diuretics for ascites control at FakirMohan Medical College and Hospital Balasore, Odisha between March 2020 and August 2023. The aetiology of liver cirrhosis included hepatitis B virus infection, hepatitis C virus infection and alcoholic liver disease. Patients who met any of the following criteria were excluded: (i) gastrointestinal (GI) bleeding within 2 weeks prior to SBP development; (ii) receiving antibiotics within 2 weeks prior to PPI use; (iii) receiving immunosuppressive therapy; (iv) recipient of a liver transplant; (v) other concurrent GI infection likely to be cause of peritonitis (e.g. liver abscess and gall-bladder rupture); and (vi) lost to follow-up. Based

on these criteria, a total of 411 patients were excluded from the study. Of these, 197 patients had undergone a liver transplantation, 166 had GI bleeding within 2 weeks prior to SBP development, 30 had a concurrent GI infection, 10 were receiving immunosuppressive therapy and eight were lost to follow-up after PPI use. Finally, a total of 1554 consecutive patients were included in the current study to reduce the effect of selection bias and potential confounders in this study, we performed rigorous adjustment for differences in baseline characteristics by using propensity score matching. After matching by propensity scores considering age, gender, aetiology of liver disease, platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), blood urea nitrogen (BUN), creatinine, serum sodium, serum albumin, serum total bilirubin, prothrombin time (PT) and Child–Pugh score, 402 patient pairs were selected. The study protocol was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board Fakirmohan medical college Balasore, Odisha.

Definitions

Patients who took any PPI for at least 1 week were included in the PPI group, while the remaining patients were placed in the non-PPI group. PPI use was divided into those using standard doses. Esomeprazole 40 mg, lansoprazole 30 mg, rabeprazole 20 mg and pantoprazole 40 mg were categorized as standard dose. Patients who took the standard doses were assigned to the group representing the dose taken group. Patients who took any H2-receptor antagonists (H2RAs) for at least 1 week were considered H2RA user. Spontaneous bacterial peritonitis was defined by an ascitic fluid polymorphonuclear (PMN) leucocyte count ≥250 cells/mm^3. Nosocomial SBP was defined as an infection that occurred >72 h after admission to the hospital, while infections diagnosed within the first 72 h of hospitalization were classified as community-acquired SBP.[23]

Data collection and assessment

The following demographical, laboratory and clinical information were collected from medical chart review: age, gender, aetiology of liver disease, platelet count, serum electrolytes, BUN, creatinine, AST, ALT, ALP, GGT, serum total bilirubin, serum albumin, PT, presence and severity of ascites and encephalopathy, ascites fluid data consisting of cell count, protein level and organism, PPI and H2RA use and time to SBP development. Ascitic fluid specimens were obtained aseptically by paracentesis and inoculated into blood culture bottles at the patient's bedside. Identification of isolates was performed using a standard identification card. With respect to PPI use, daily dose and indications were investigated. In the PPI group, time interval to SBP after start and end of PPI use was also determined. We could collect exact data pertaining to PPI use from the chart review because the enrolled patients regularly visited the hospital for the screening of hepatocellular carcinoma. Spontaneous bacterial peritonitis incidence rate was the primary outcome. As a secondary outcome, the characteristics of SBP were evaluated in terms of organisms isolated from the ascitic fluid, presence or absence of sepsis, length of hospital stay and in-hospital mortality. SBP incidence was compared between the two groups in all study subjects and propensity score matched cohort.

Statistical analysis

In all study subjects, continuous variables were compared parametrically using Student's t-test. The propensity scores were estimated regarding all variables presented in the baseline characteristics with parsimonious logistic regression model. One to one calliper matching without replacement was performed within 25% of the standard deviation of log-transformed propensity scores. The balance of the matched cohort was evaluated using standardized mean difference and hypothetical test. In the propensity score matched cohort, the two groups were compared in terms of baseline characteristics. Multivariate analysis was performed on variables that were associated with SBP incidence based on univariate analysis ($P < 0.200$). Hazard ratios (HRs) were presented together with the 95% confidence interval (CI) Statistical results are presented as the mean S.D. median (interquartile range) or number of patients (%).

RESULTS

Baseline characteristics of the study population before matching

Among the 1554 patients included in the study, the mean age was 57.9±10.1 years and 1151 patients (74.1%) were male. A total of 512 patients (32.9%) were included in the PPI group and the remaining 1042 (67.1%) were included in the non-PPI group. The aetiology of liver disease was hepatitis B virus infection in 1175 patients (75.6%), hepatitis C virus infection in 262 patients (16.9%) and alcoholic liver disease in 117 patients (7.5%). The mean Child–Pugh score was 7.8±1.7: 359 patients (23.1%) were Child–Pugh class A, 936 (60.2%) were class B and 259 (16.7%) were class C. The baseline characteristics of the PPI and non-PPI groups are summarized in Table 1. There were no significant differences between the two groups with respect to age, gender, aetiology of liver disease, AST, ALP, GGT, creatinine and Child–Pugh score. However, the PPI group exhibited a lower platelet count (91.5, 54.6 vs. 102.0 62.4, P = 0.001), ALT (47.5, 51.4 vs. 57.5, 79.4, P = 0.003) and serum sodium level (136.6 5.5 vs. 138.3 4.6, $P < 0.001$) and higher BUN (18.0 13.3 vs. 15.6 9.2, $P < 0.001$), albumin (3.2 0.6 vs. 3.1 0.6, P = 0.038), bilirubin (3.0 5.0 vs. 2.4 4.5, P = 0.049) and PT level (1.4 0.4 vs. 1.3 0.3, P = 0.003) than the non-PPI group.

Table 1: Comparison of baseline characteristics between proton pump inhibitor (PPI) group (n = 512) and non-PPI group (n = 1042) in all study subjects (n = 1965)

Variables	PPI group (n = 512)	Non-PPI group (n = 1042)	P value
Age (years)	58.0 ± 10.1	57.8 ± 10.2	0.702
Gender, male	384 (75.0)	767 (73.6)	0.556
Aetiology of liver disease			
HBV	384 (75.0)	791 (75.9)	0.527
HCV	84 (16.4)	178 (17.1)	
Alcohol	44 (8.6)	73 (7.0)	
Platelet count (x10^3 /mm^3)	91.5± 54.6	102.0 ± 62.4	0.001
AST (IU/L)	73.8 ± 86.0	84.0±114.0	0.073
ALT (IU/L)	47.5 ±51.4	57.5 ± 79.4	0.003
ALP (IU/L)	126.7± 82.0	129.7 ± 109.5	0.580
GGT (IU/L)	90.0±105.7	104.7 ±150	0.062
Creatinine (mg/dL)	1.1 ± 0.9	1.0 ±0.7	0.069
Albumin (g/dL)	3.2± 0.6	3.1 ± 0.6	0.038
Prothrombin time (INR)	1.4 ± 0.4	1.3 ± 0.3	0.003
Child–Pugh score	7.9 ± 1.8	7.8 ±1.6	0.079

HBV, hepatitis B virus; HCV, hepatitis C virus; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; BUN, blood urea nitrogen. Data are shown as the mean ± S.D. or number (%) of patients

SBP incidence of the study population before matching.

During a follow-up of 847 person-years (mean 19.8 20.6 months) and 2526 person-years (29.0 28.9 months), 90 and 146 patients had SBP in the PPI and non-PPI groups respectively. The calculated annual SBP incidence rates in the PPI and non-PPI groups were 10.6% and 5.8% respectively. The cumulative SBP incidence rate was higher in the PPI group than in the non-PPI group (P = 0.002, by log-rank test;

Baseline characteristics of the propensity score matched cohort.

In the propensity score matched cohort, there were no significant differences between the two groups regarding age, gender, aetiology of liver disease, platelet count, AST, ALT, ALP, GGT, BUN, creatinine, serum sodium level, albumin, bilirubin, PT and Child–Pugh score (Table 2).

Incidence and characteristics of SBP in the propensity score matched cohort.

During a follow-up of 684 person-years (mean 20.4 20.8 months) and 1000 person-years (29.8, 29.0 months), 74 and 60 patients had SBP in the PPI and non-PPI groups respectively. The calculated annual SBP incidence rates in the PPI and non-PPI group were 10.8% and 6.0% respectively. The cumulative SBP incidence rate was higher in the PPI group than in the non-PPI group (P = 0.038, by the clustered Cox regression). The characteristics of SBP are summarized in Table 3. Among all cases of SBP, the proportion of nosocomial infections was similar between the PPI and non-PPI groups, at 36.5% and 31.7% respectively (P = 0.559). Sepsis accompanied 12.2% and 10.0% of cases of SBP in the PPI and non-PPI groups respectively (P = 0.693). The PMN leucocyte count and protein level in ascites fluid did not differ between the two groups. Organisms were isolated from the ascitic fluid with a similar frequency between the PPI and non-PPI groups (33.8% vs. 30.0%, P = 0.641). Escherichia coli was the most common isolate in both groups [12] isolates (48%) in the PPI group and seven (38.9%) in the non-PPI group], followed by Klebsiella species [five isolates (20%)] in the PPI group and Streptococcus species [three isolates (16.7%)] in the non-PPI group. Although Gram-negative organisms were isolated more frequently in the PPI group than in the non-PPI group, the difference did not reach statistical significance (84.0% vs. 72.2%, P = 0.090).

Comparison of clinical outcomes in the propensity score matched cohort.

The length of hospital stay did not differ between the two groups [PPI group vs. non-PPI, 17.0 (9.8–32.8) vs. 16.0 (11–26.8), P = 0.448; Table 3]. In-hospital mortality in PPI group was not significantly higher than in nonPPI group (PPI group vs. non-PPI, 6.5% vs. 3.7%, P = 0.078; Table 3).

Multivariate analysis for the association of PPI use with SBP.

To adjust for simultaneous impact of potential confounders, Cox proportional hazards regression was conducted (Table 4). In the univariate analysis, gender, Child–Pugh score, BUN, serum sodium and PPI use was associated with SBP development. Multivariate analysis revealed that male gender (HR 1.849; 95% CI: 1.307– 2.616; P = 0.001), Child–Pugh score (HR 1.352; 95% CI: 1.241–1.472; P < 0.001), serum sodium (HR 0.958; 95% CI: 0.931–0.986; P = 0.003) and PPI use (HR 1.396; 95% CI: 1.057–

1.843, P = 0.019) were independent risk factors for SBP development.

Details of PPI use in the PPI group.

Among 512 PPI users, 192 patients received PPI for nonspecific symptoms, while indications were well documented in 320 patients. Of the latter group, peptic ulcer disease (194, 59.1%) was the most common indication for PPI use, followed by conditions related to oesophageal variceal ligation (91, 27.7%) and GERD (35, 10.7%). Indications for PPI use was similar between patients with and without SBP (P = 0.170). In patients with SBP, the mean duration of PPI use was 74.4 - 88.8 days. Of them, 40/90 patients (44.4%) developed SBP when PPI was used continuously, 25 (27.8%) did within 90 days from the end of PPI use and 25 (27.8%) beyond 90 days from the end of PPI use.

Table 2: Comparison of baseline characteristics between PPI group (n = 402) and non-PPI group (n = 402) in the propensity score matched cohort (402 matched pairs)

Variables	PPI group (n = 402)	Non-PPI group (n = 402)	P value
Age, years	57.8 ± 10.2	57.7 ±9.5	0.821
Gender, male	302 (75.1)	307 (76.4)	0.739
Aetiology of liver disease			
HBV	316 (78.6)	316 (78.6)	1.000
HCV	57 (14.2)	57 (14.2)	
Alcohol	29 (7.2)	29 (7.2)	
AST (IU/L)	74.2±86.5	70.9 ±58.0	0.533
ALP (IU/L)	127.5± 81.4	125.5 ±144.2	0.809
GGT (IU/L)	93.6±109.4	90.9 ± 171.5	0.784
BUN (mg/dL)	16.3 ± 10.1	16.3 ± 10.0	0.999
Creatinine (mg/dL)	1.0 ± 0.6	1.0 ±0.8	0.571
Sodium (mmol/L)	137.3 ± 4.8	137.6 ± 5.1	0.291
Albumin (g/dL)	3.2 ±0.6	3.2 ±0.6	0.696
Prothrombin time (INR)	1.4 ±0.4	1.4 ± 0.3	0.655
Child–Pugh score	7.9 ± 1.6	7.9 ±1.7	0.819

PPI, proton pump inhibitor; HBV, hepatitis B virus; HCV, hepatitis C virus; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; BUN, blood urea nitrogen.; Data are shown as the mean ± S.D. or number (%) of patients.

Table 3: Comparison of SBP characteristics between PPI and non-PPI groups in the propensity score matched cohort (402 matched pairs)

Variables Type of SBP	PPI group (n = 74)	Non-PPI group (n = 60)	P value
Nosocomial	27 (36.5)	19 (31.7)	0.559
Community-acquired	47 (63.5)	41 (68.3)	
Ascites protein (g/dL)	1.2±0.8	0.9 ±0.8	0.074
Isolated organisms	25 (33.8)	18 (30.0)	0.641
Gram-negative	21 (84.0)	13 (72.2)	0.090
Escherichia coli	12	7	
Klebsiella species	5	2	
Aeromonas species	1	1	
Others	3		
Gram-positive	4 (16.0) 5 (27.8)	3	
Streptococcus species	3 3		
Enterococcus species	1 1		
Presence of sepsis	9 (12.2)	6 (10.0)	0.693
Hospital stays (day)	17.0 (9.8–32.8)	16.0 (11–26.8)	0.448
In-hospital mortality	26 (6.5)	15 (3.7)	0.078

PPI, proton pump inhibitor; SBP, spontaneous bacterial peritonitis; PMN, polymorphonuclear. Data are shown as the mean±S.D. median (interquartile range) or number (%) of patients.

Table 4: Multivariate analysis for the association of PPI use with SBP

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)	1.005 (0.992–1.018)	0.432		
Gender				
Female	1		1	
Male	1.848 (1.327–2.572)	< 0.001	1.849 (1.307–2.616)	0.001
Aetiology of liver disease				
HBV	1			
HCV	1.146 (0.827–1.587)	0.413		
Alcohol	0.833 (0.499–1.390)	0.484		
Child–Pugh score	1.462 (1.361–1.571)	<0.001	1.352 (1.241–1.472)	<0.001
Platelet count ($X10^3$ /mm^3)	0.998 (0.995–1.001)	0.127	1.000 (0.997–1.002)	0.825
GGT (IU/L)	1.000 (1.000–1.001)	0.261		
BUN (mg/dL)	1.012 (1.001–1.023)	0.027	1.001 (0.990–1.013)	
Creatinine (mg/dL)	1.032 (0.886–1.202)	0.685		
Sodium (mmol/L)	0.916 (0.897–0.935)	< 0.001	0.958 (0.931–0.986)	
H2RA use	0.923 (0.703–1.214)	0.568		
PPI use	1.510 (1.159–1.967)	0.002	1.396 (1.057–1.843)	

PPI, proton pump inhibitor; SBP, spontaneous bacterial peritonitis; HR, hazard ratio; CI, confidence interval; H2RA, H2-receptor antagonist

In terms of PPI dose, a standard dose was used by 188 patients (36.7%), while a half dose was used by 324 patients (63.3%). In addition, the dose of PPI was similar between patients with and without SBP (P = 0.152). According to multivariate Cox regression analysis in the PPI group, PPI dose was not an independent risk factor for SBP (standard dose vs. half dose, HR 2.184, 95% CI 0.935–5.103, P = 0.071) after correction for gender, Child–Pugh score and serum sodium.

DISCUSSION

Small intestinal bacterial overgrowth is a predisposing factor to SBP in patients with cirrhosis.[13–15] PPI use may increase bacterial overgrowth within the GI tract.[18, 25] Thus PPI use has been proposed to contribute to SBP.[19, 20] However, this is based on findings from case– control studies, often consisting of a small series. Bajaj et al.[19] reported that PPI use is associated with SBP in patients with advanced cirrhosis. In their study, 70 cirrhotic patients with SBP were compared with 70 cirrhotic patients without SBP matched for Child–Pugh score and age. Goel et al.[26] found that subjects who had not taken PPIs within the past 90 days were almost 70% less likely to develop SBP than those who had taken PPIs in the previous 7 days. Their study was based on 130 hospitalized cirrhotic patients consisting of 65 SBP patients and 65 controls matched for Child–Pugh score. Because of the nature of case–control studies, it is not possible to establish causality based on these results. In addition, Campbell et al.[21] reported that PPI use is not associated with SBP. These results might be confounded by several factors, and thus there is a significant need to clearly demonstrate causation. Therefore, we performed a large retrospective cohort study to determine whether PPI use increases the risk of SBP development in cirrhotic patients with ascites. In addition, we performed extensive matching for liver function to consider that PPIs might be more commonly used by patients with worse liver function which is a predisposing factor to SBP.[27, 28] Following matching, none of the differences in baseline characteristics between the two groups remained. In addition, we considered H2RA use as a potential confounder and conducted multivariate analysis to exam the association of PPI use with SBP. Our results showed that SBP incidence was higher in the PPI group than in the non-PPI group before and after matching. In the current study, PPI user was defined as patients who took any PPI for at least 1 week. The steady maximum mean percentage time of gastric pH>4 was seen after taking PPI for 7 days.[29] Nevertheless, 1 week of PPI use is not a long-term treatment and is rather arbitrary. However, we have showed that even 1 week of PPI use increases the incidence of SBP in patients with ascites. Considering a significant number of PPI user with an inappropriate indication in this study population, even short-term PPI use, without a definite indication, should be avoided in cirrhotic patients with ascites. In addition, we showed that SBP similarly occurs between the standard and half dose PPI users. According to the recent US survey regarding the treatment patterns for GERD, 71.0% used PPIs once a day, 22.2% used twice a day and 6.8% more than twice a day or on an as-needed basis.[30] Thus, it would be more clinically relevant to know if double dose PPI use carried a higher risk of SBP than half dose. Unfortunately, however, the comparison could not be performed because only six patients took double dose PPI during an even short period in the current study population. Established risk factors reported for SBP in cirrhotic patients include low ascitic fluid protein concentration, decreased prothrombin activity and increased serum bilirubin level.[31,32–34] At our institution,

ascitic fluid analysis is not routinely performed for cirrhotic patients with new-onset ascites, and thus ascitic fluid protein concentration could not be included in baseline characteristics. To overcome this limitation, we performed extensive matching for liver function by propensity scores. In addition, protein level in ascites was measured in patients with SBP, and it did not differ between the PPI and the non-PPI groups. Moreover, other markers of advanced liver dysfunction such as episode of encephalopathy and refractory ascites were compared between the two groups in the matched cohort and no significant differences were found (data not shown). These observations support that PPI use increases the risk of SBP development regardless of the severity of liver function impairment. In contrast to liver dysfunction, nonselective b-blockers and antibiotic prophylaxis can reduce the chance of SBP development.[35–37] Although those medications were not matched in the current study, no significant differences were found with regard to the use of nonselective b-blockers and antibiotic prophylaxis in the matched cohort (data not shown). Our study population included many early cirrhotic patients with Child–Pugh class A (359, 23.1%), which may stem from our exclusion of patients who had undergone liver transplantation or had GI bleeding within 2 weeks prior to SBP development. For similar reasons, the HR (1.396) of PPI use was relatively lower than the odds ratios (3.443–4.31) reported in the previous studies.[19, 38] However, because Child–Pugh score was shown to be the independent risk factor for SBP, increased caution is needed with respect to PPI use in patients with Child–Pugh class B and C. In the current study, bacteriological confirmation was available in 43/134 patients (32.1%) even using bedside inoculation of ascites into blood culture bottles for increased sensitivity.[39] A large proportion of our SBP patients had Gram-negative infections. When comparing bacterial epidemiology, Gram-negative infections were more frequent in the PPI group than in the non-PPI group, although the difference did not reach statistical significance (P = 0.090). Interestingly, E. coli and Klebsiella species accounted for the increased Gram-negative infections in the PPI group. It has been known that only a few intestinal bacteria are able to translocate into mesenteric lymph nodes, which include E. coli and Klebsiella pneumoniae and other Enterobacteriaceae.[40] BT is the most common cause of SBP,[12] and SIBO has been linked with pathologic BT.[14, 15] Considering PPI use has been proposed to facilitate SIBO, our bacteriological findings also support the possibility that PPI use plays an important role in the pathophysiology of SBP. Proton pump inhibitor use also has a link with other infection. Clostridium difficile infection (CDI) has been shown to be possibly associated with PPI use.[41, 42] On the contrary to SBP, however, the pathophysiology of CDI by PPI use remains unclear because acidic gastric content does not kill C. difficile spores.[43] In addition, the association between CDI and PPI use may be exaggerated due to the comorbidities in PPI users.[7, 44] Therefore, well designed prospective cohort study is clearly needed to assess the true impact of PPI use on CDI development in the future. The association between pneumonia and PPI use is also still being debated. Recently, however, de Jager et al.[46] showed that PPI use increased the risk of community-acquired pneumonia due to Streptococcus pneumoniae more than twofold in a prospective cohort study. The plausible relevant mechanism is that decreased gastric acidity could promote proliferation and subsequent translocation of swallowed oropharyngeal flora. Confounding factors using rigorous propensity score matching and specific exclusion criteria. Fourth, we analysed the relationship of PPI dose and SBP risk. Lastly, we evaluated the bacterial epidemiology of SBP in PPI users.

CONCLUSION

PPI use significantly increases the risk of SBP in cirrhotic patients with ascites. Therefore, PPI use should be undertaken with greater caution in cirrhotic patients with other risk factors for SBP. Also, PPI should be used with appropriate indications and duration.

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REFERENCES

1. Targownik LE, Metge C, Roos L, Leung S. The prevalence of and the clinical and demographic characteristics associated with high-intensity proton pump inhibitor use. Am J Gastroenterol 2007; 102: 942–50.
2. Wolfe MM, Soll AH. The physiology of gastric acid secretion. N Engl J Med 1988; 319: 1707–15.
3. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol 2013; 108: 308–28; quiz 329.
4. Poynard T, Lemaire M, Agostini H. Meta-analysis of randomized clinical trials comparing lansoprazole with ranitidine or famotidine in the treatment of acute duodenal ulcer. Eur J Gastroenterol Hepatol 1995; 7: 661–5.
5. Dekkers CP, Beker JA, Thjodleifsson B, Gabryelewicz A, Bell NE, Humphries TJ. Comparison of rabeprazole 20 mg versus omeprazole 20 mg in thetreatment of active duodenal ulcer: a European multicentre study. Aliment Pharmacol Ther 1999; 13: 179–86.
6. Bader JP, Delchier JC. Clinical efficacy of pantoprazole compared with ranitidine. Aliment Pharmacol Ther 1994; 8(Suppl. 1): 47–52.
7. Tleyjeh IM, Bin Abdulhak AA, Riaz M, et al. Association between proton pump inhibitor therapy and Clostridium difficile infection: a contemporary systematic review and meta-analysis. PLoS ONE 2012; 7: e50836.

8. Johnstone J, Nerenberg K, Loeb M. Meta-analysis: proton pump inhibitor use and the risk of community-acquired pneumonia. Aliment Pharmacol Ther 2010; 31: 1165–77.
9. Yu EW, Bauer SR, Bain PA, Bauer DC. Proton pump inhibitors and risk of fractures: a meta-analysis of 11 international studies. Am J Med 2011; 124: 519–26.
10. Ho PM, Maddox TM, Wang L, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. JAMA 2009; 301: 937–44.
11. Wiest R, Krag A, Gerbes A. Spontaneous bacterial peritonitis: recent guidelines and beyond. Gut 2012; 61: 297–310.
12. Wiest R, Garcia-Tsao G. Bacterial translocation (BT) in cirrhosis. Hepatology 2005; 41: 422–33.
13. Bauer TM, Steinbruckner B, Brinkmann FE, et al. Small intestinal bacterial overgrowth in patients with cirrhosis: prevalence and relation with spontaneous bacterial peritonitis. Am J Gastroenterol 2001; 96: 2962–7.
14. Guarner C, Runyon BA, Young S, Heck M, Sheikh MY. Intestinal bacterial overgrowth and bacterial translocation in cirrhotic rats with ascites. J Hepatol 1997; 26: 1372–8.
15. Pardo A, Bartoli R, Lorenzo-Zuniga V, et al. Effect of cisapride on intestinal bacterial overgrowth and bacterial translocation in cirrhosis. Hepatology 2000; 31: 858–63.
16. Ramachandran A, Prabhu R, Thomas S, Reddy JB, Pulimood A, Balasubramanian KA. Intestinal mucosal alterations in experimental cirrhosis in the rat: role of oxygen free radicals. Hepatology 2002; 35: 622–9.
17. Obstein KL, Campbell MS, Reddy KR, Yang YX. Association between model for end-stage liver disease and spontaneous bacterial peritonitis. Am J Gastroenterol 2007; 102: 2732–6.
18. Lewis SJ, Franco S, Young G, O'Keefe SJ. Altered bowel function and duodenal bacterial overgrowth in patients treated with omeprazole. Aliment Pharmacol Ther 1996; 10: 557–61.
19. Bajaj JS, Zadvornova Y, Heuman DM, et al. Association of proton pump inhibitor therapy with spontaneous bacterial peritonitis in cirrhotic patients with ascites. Am J Gastroenterol 2009; 104: 1130–4.
20. Trikudanathan G, Israel J, Cappa J, O'Sullivan DM. Association between proton pump inhibitors and spontaneous bacterial peritonitis in cirrhotic patients – a systematic review and meta-analysis. Int J Clin Pract 2011; 65: 674–8.
21. Campbell MS, Obstein K, Reddy KR, Yang YX. Association between proton pump inhibitor use and spontaneous bacterial peritonitis. Dig Dis Sci 2008; 53: 394–8.
22. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a nonrandomized control group. Stat Med 1998; 17: 2265–81.
23. Cheong HS, Kang CI, Lee JA, et al. Clinical significance and outcome of nosocomial acquisition of spontaneous bacterial peritonitis in patients with liver cirrhosis. Clin Infect Dis 2009; 48: 1230–6.
24. Hill J. Discussion of research using propensity-score matching: comments on 'A critical appraisal of propensityscore matching in the medical literature between 1996 and 2003' by Peter Austin, Statistics in Medicine. Stat Med 2008; 27: 2055–61; discussion 2066–9.
25. Chang CS, Chen GH, Lien HC, Yeh HZ. Small intestine dysmotility and bacterial overgrowth in cirrhotic patients with spontaneous bacterial peritonitis. Hepatology 1998; 28: 1187–90.
26. 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. Clin Gastroenterol Hepatol 2012; 10: 422–7.
27. Caruntu FA, Benea L. Spontaneous bacterial peritonitis: pathogenesis, diagnosis, treatment. J Gastrointest Liver Dis 2006; 15: 51–6. 2.
28. Sheer TA, Runyon BA. Spontaneous bacterial peritonitis. Dig Dis 2005; 23: 39–46
29. Miner PB Jr, Allgood LD, Grender JM. Comparison of gastric pH with omeprazole magnesium 20.6 mg (Prilosec OTC) o.m. famotidine 10 mg (Pepcid AC) b.d. and famotidine 20 mg b.d. over 14 days of treatment. Aliment Pharmacol Ther 2007; 25: 103–9
30. Chey WD, Mody RR, Wu EQ, et al. Treatment patterns and symptom control in patients with GERD: US community-based survey. Curr Med Res Opin 2009; 25: 1869–78.
31. Lee KJ, Kim JI, Park JS, et al. Practice pattern of gastroenterologists for the management of GERD under the minimal influence of the insurance reimbursement guideline: a multicenter prospective observational study. J Korean Med Sci 2011; 26: 1613–8
32. Tito L, Rimola A, Gines P, Llach J, Arroyo V, Rodes J. Recurrence of spontaneous bacterial peritonitis in cirrhosis: frequency and predictive factors. Hepatology 1988; 8: 27–31.
33. . Llach J, Rimola A, Navasa M, et al. Incidence and predictive factors of first episode of spontaneous bacterial peritonitis in cirrhosis with ascites: relevance of ascitic fluid protein concentration. Hepatology 1992; 16: 724–7
34. Andreu M, Sola R, Sitges-Serra A, et al. Risk factors for spontaneous bacterial peritonitis in cirrhotic patients with ascites. Gastroenterology 1993; 104: 1133–8.
35. Senzolo M, Cholongitas E, Burra P, et al. Beta-blockers protect against spontaneous bacterial peritonitis in cirrhotic patients: a meta-analysis. Liver Int 2009; 29: 1189–93.
36. Fernandez J, Navasa M, Planas R, et al. Primary prophylaxis of spontaneousbacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. Gastroenterology 2007; 133: 818–2
37. Gines P, Rimola A, Planas R, et al. Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis: results of a double-blind, placebo-controlled trial. Hepatology 1990; 12: 716–24.
38. Choi EJ, Lee HJ, Kim KO, et al. Association between acid suppressive therapy and spontaneous bacterial peritonitis in cirrhotic patients with ascites. Scand J Gastroenterol 2011; 46: 616–20.
39. Castellote J, Xiol X, Verdaguer R, et al. Comparison of two ascitic fluid culture methods in cirrhotic patients with spontaneous bacterial peritonitis. Am J Gastroenterol 1990; 85: 160

40. Wells CL. Relationship between intestinal microecology and the translocation of intestinal bacteria. Antonie Van Leeuwenhoek 1990; 58: 87–93.

41. Linsky A, Gupta K, Lawler EV, Fonda JR, Hermos JA. Proton pump inhibitors and risk for recurrent Clostridium difficile infection. Arch Intern Med 2010; 170: 772–8.

42. Yearsley KA, Gilby LJ, Ramadas AV, Kubiak EM, Fone DL, Allison MC. Proton pump inhibitor therapy is a risk factor for Clostridium difficile-associated diarrhoea. Aliment Pharmacol Ther 2006; 24: 613–9.

43. Nerandzic MM, Pultz MJ, Donskey CJ. Examination of potential mechanisms to explain the association between proton pump inhibitors and Clostridium difficile nfection. Antimicrob Agents Chemother 2009; 53: 4133–7.

44. Leontiadis GI, Miller MA, Howden CW. How much do PPIs contribute to C. difficile infections? Am J Gastroenterol, 2012; 107: 1020–1.

45. Sarkar M, Hennessy S, Yang YX. Proton-pump inhibitor use and the risk for community-acquired pneumonia. Ann Intern Med, 2008; 149: 391–8

46. De Jager CP, Wever PC, Gemen EF, et al. Proton pump inhibitor therapy predisposes to community-acquired Streptococcus pneumoniae pneumonia. Aliment Pharmacol Ther, 2012; 36: 941–9.

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