Association between Proton Pump Inhibitors Use and Spontaneous Bacterial Peritonitis Development in Egyptian Cirrhotic Patients with Ascites

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Background and study aim: Spontaneous bacterial peritonitis (SBP) is a frequent complication in cirrhotic patients with ascites with significant morbidity and mortality. In patients with liver disease, there are many indications for acid suppressive therapy. Proton pump inhibitors (PPIs) are the most frequently prescribed drugs for acid suppression in patients with cirrhosis. Several studies evaluating the risk of SBP in patients on PPIs use have shown conflicting results. This study aimed at exploring whether PPIs use in Egyptian cirrhotic patients with ascites is associated with spontaneous bacterial peritonitis development.

Patients and Methods: The study included 209 patients with liver cirrhosis and ascites. According to ascitic fluid polymorphonuclear leucocyte (PMN) cell count, patients were allocated into: SBP group (PMN $\geq$ 250 cell/ mm^3), and non-SBP group (PMN < 250 cell/ mm^3). Both groups were compared to each other as regards rate of PPIs use, PPIs types and their indication.

Results: Out of 209 cirrhotic patients with ascites, SBP was detected in 34.9% of patients whether they were on PPIs or not. SBP patients had a significant higher use of PPIs therapy (72.6%) than the non-SBP patients (26.5%) (P<0.001). However, there was no statistical significant difference regarding type of PPIs or indications of use (P>0.05).

Conclusion: The rate of PPIs use was higher in SBP patients than in patients without SBP. There were no differences regarding PPIs types or indications of use between both groups. Thus, PPIs therapy should be judiciously used and only when indicated in patients with liver cirrhosis and ascites.

INTRODUCTION

Spontaneous bacterial peritonitis (SBP) is a frequent complication in cirrhotic patients with ascites, which is associated with significant morbidity and increased mortality **[1,2]**. SBP is defined as infection of the ascitic fluid in the absence of any obvious source of infection and/or an intra-abdominal inflammatory focus. Around 50% of SBP episodes are diagnosed at the time of hospital admission while the remainder 50% is acquired during the hospitalization period. The significant morbidity and mortality rates associated with SBP make it critical to prompt early diagnosis and identify the predisposing factors **[3,4,5]**.

Small intestinal bacterial overgrowth (SIBO) appears to be a predisposing factor to ascitic fluid infection in patients with advanced liver disease. It has been shown that patients with SBP had higher prevalence of SIBO than ascitic patients who had no evidence of ascitic fluid infection **[6]**. Patients with advanced liver disease are more liable to SIBO due to weakened GIT immunity, disturbed GIT motility as well as prolonged acid suppression **[7]**.

In patients with liver disease there are so many indications for acid suppressive therapy such as, gastro-

esophageal reflux disease (GERD), peptic ulcer disease, Barrett's esophagus, after endoscopic management of esophageal varices to prevent recurrent bleeding and/or scelerosant and post-banding ulcer **[8]**. Proton pump inhibitors (PPIs) are the most frequently used drugs for acid suppression. However, suppression of gastric acid by these medications has been associated with several potential adverse enteric infections (*Clostridium difficile*, *Klebsiella spp*., *Salmonella spp*.) and community-acquired pneumonia **[6,9]**. Acid-suppressive therapy is also known to predispose to bacterial overgrowth within the gastrointestinal tract and translocation across the epithelial barrier of the intestine **[6]**. Studies have shown the appearance of SIBO after PPIs use, to which cirrhotic patients are predisposed to given the abnormal intestinal motility and neuro-hormonal imbalance in the gut environment **[10,11,12]**. There is also evidence that PPIs have depressive effects on neutrophil action and innate immunity, adding a direct anti-inflammatory component to this predisposition **[13]**. The aim of the study is to explore whether PPIs use in Egyptian cirrhotics patients with ascites is associated with spontaneous bacterial peritonitis development.

PATIENTS AND METHODS

Patients

The study was conducted in Tropical Medicine and Medical Microbiology and Immunology Departments, Zagazig University Hospitals, Egypt. Over one year period, the study included total number of 209 patients (112 males and 97 females) who have liver cirrhosis and ascites, their ages ranged from 38 to 65 years.

Study Design

Cross sectional study

Inclusion criteria:

Adult patients of both genders who have liver cirrhosis and ascites were offered to be enrolled in the study. The patients who gave an informed written consent were divided into 2 groups according to their ascitic fluid polymorphonuclear leucocyte (PMN) cell count:

- **SBP group** (73 patients)**:** Patients with paracentesis-proven SBP (PMN≥250 cell/ mm^3), with or without positive ascitic fluid culture.
- **Non-SBP group** (136 patients)**:** Patients with no evidence of ascitic fluid infection (PMN<250cell/mm^3), with negative ascitic fluid culture.

Exclusion Criteria

At least 2 weeks prior to hospital admission, all patients who received antibiotics or who had GIT bleeding; GIT endoscopy or any invasive abdominal procedures as (catheterization, cannulation, paracentesis) were excluded from the study. Furthermore, patients with secondary peritonitis, non-cirrhotic ascites as well as patients with previous history of SBP and HCC were excluded from the study.

All patients were subjected to the following: (a) full medical history taking including history of PPIs use (patients were considered PPI users if they are using a PPI daily for at least 2 weeks before hospital admission), and its therapeutic indication; **(b) complete physical examination:** the stigmata of liver disease, the clinical manifestations suggestive of ascitic fluid infection**; (c) Laboratory tests** including complete blood count, Liver function tests, kidney function tests, coagulation profile and ascitic fluid analysis (cytologically, biochemically and bacteriologically), Alpha-feto protein; **(d) Modified Child–Turcotte–Pugh (CTP) score [14]**; **(e) Pelvi-abdominal ultrasonography** with stress on liver cirrhosis & its complications; **(f) Chest X-ray** and **(g) Complete urine analysis.**

Statistical analysis:

Data were checked, entered and analyzed using SPSS (Statistical Package for the Social Sciences) version 19. Data were expressed as mean ± SD for quantitative variable, number and percentage for qualitative one. Chi-squared (X^2), t test were used when appropriate. P-value <0.05 was considered significant.

RESULTS

Patient characteristics

Out of all included cirrhotic patients with ascites (209 patients), SBP was detected in 73 (34.9%) patients whether they were on PPIs or not. **Table 1** shows the comparison of the demographic and baseline characteristics of both groups. There were no statistical significant differences between the studied groups as regards age and gender distribution (*P* =0.29 and 0.79

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respectively). All of the patients in both groups were Child-Pugh class (B) or (C) with no statistical significant difference (*P* =0.1). No cases were classified as Child-Pugh class (A).

Ascitic fluid parameters

As regard laboratory parameters **(Table 1)**, total leucocytic count (TLC), in both blood and ascitic fluid, and PMN leucocyte cell count in the ascitic fluid were statistically significant higher in SBP patients (*P* <0.001). Among SBP patients, ascitic fluid culture revealed positive results in 60.2% (44 out of 73 patients) of cases **(Figure 1)**.

Parameters of PPIs use

Table 2 shows PPIs use among both studied groups which revealed that SBP patients had a significant higher use for PPIs (72.6%) than the non-SBP patients (26.5%) (*P* <0.001). In the current study PPIs were used for judicious specific indications for more than 2 weeks, and different generations of PPIs were used. As expected the most common indication of use was related to endoscopic management of varices **(as shown in Figure 2 and Table 2)**. However, there was no statistical significant difference as regards type of PPIs or indications of PPIs use (*P* >0.05) between patients with and without SBP.

Table (1): Demographic and baseline characteristics of both studied groups.

	SBP (n.=73)	Non- SBP (n.=136)	P value
Age (years)			
Mean±SD	49.4±7.74	51.5±8.08	0.29
Gender			
Male	40 (54.8%)	72 (52.9%)	0.79
Female	33 (45.2%)	64 (47.1%)	
Child-Pugh score			
B	8 (10.95%)	27 (19.9%)	0.1
C	65(89.04%)	109 (80.1%)	
Laboratory parameters			
TLC (Cell/ m³)	6.5±2.0	5.4±2.5	<0.001*
Hb (g/dl)	9.6±1.7	9.4±1.4	0.6
Platelet (Cell/ m³)	102.5±47.8	103.3±39. 2	0.9
Total bilirubin (mg/dl)	2.7±2.5	2.3±2.2	0.09
Direct bilirubin (mg/dl)	1.76±1.7	1.5±1.7	0.07
Total protein (g/dl)	6.7±0.8	6.6±0.8	0.24
Serum albumin (g/dl)	2.38±0.5	2.4±0.5	0.54
ALT (U/L)	42.9±16.8	41.9±16.8	0.55
AST (U/L)	53.0±18.8	53.5±19.1	0.86
Prothrombin concentration	51.4 ±15	52.4±16.5	0.68
INR	1.48±0.35	1.56±0.39	0.26
Creatinine (mg/dl)	1.06±0.5	1.12±0.4	0.34
Ascitic fluid analysis			
Glucose (mg/dl)	129±69.4	115.8±42	0.1
Protein (mg/dl)	1205.5±231.5	1362.1±695	0.06
LDH (IU/L)	125.5±63.1	139.3±85	0.22
TLC (Cell/ m³)	895 ±350	220±103	<0.001*
PMN(Cell/m³)	700 ±520	119.1±57.0	<0.001*

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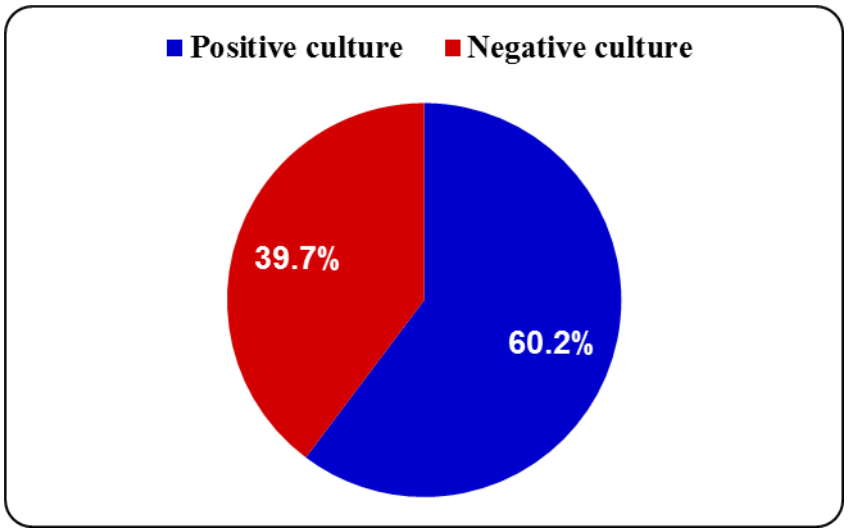

Figure (1): Ascitic fluid culture results in SBP group

Table (2): Proton pump inhibitors (PPIs) use among both studied groups.

	SBP (n.=73)	Non-SBP (n.=136)	P value
PPI use			
PPI users	53 (72.6%)	36 (26.5%)	<0.001*
Non-PPI users	20 (27.4%)	100 (73.5%)	
Types of PPI used			
Omeprazol	29 (54.7%)	20 (55.6%)	
Pantoprazole	15 (28.3%)	9 (25.0%)	0.81
Rabiprazol	5 (9.43%)	4 (11.1%)	
Esomoprazole	4 (7.5%)	3 (8.33%)	
Indications of PPI use			
GRED	20 (37.3%)	10 (27.7%)	0.32
Peptic ulcer	13 (24.5%)	5 (13.8%)	0.22
Post EBL or EST	16 (30.1%)	16 (44.4%)	0.16
Dyspepsia	4 (7.54%)	5 (13.8%)	0.53

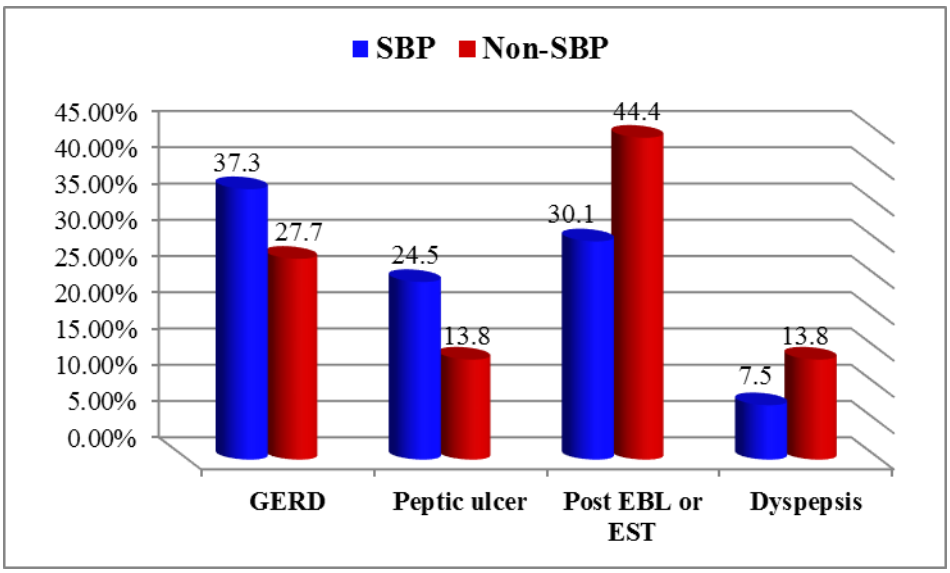

Figure (2): Indications of PPIs use in both groups.

DISCUSSION

The present study revealed that the frequency of SBP in cirrhotic ascitic patients was 34.9% whether they were on PPIs or not, with most of the SBP patients were classified as CTP-class C (89.0%). These results agree with previous studies which reported that frequency of SBP is ranged from 10-30% in patients with advanced liver cirrhosis **[4,15,16]**. Other studies showed that majority of SBP patients have advanced liver disease and 72.7% were CTP-class C **[17,18]**. Similar figures were obtained from a recently published article focusing similar cohort of Egyptian patients with SBP frequency of 62% **[19]**. However, the latter study enrolled only 100 cirrhotic patients in comparison to 209 patients in our study.

In the current study, it was found that patients with SBP had a significantly higher rate of PPIs use (72.6%) compared with non-SBP patients (26.5%) (*P* <0.001), a result supports an association between SBP development and PPIs use in cirrhotic ascitic patients. This finding agrees with several studies **[20,21,22]** which support direct correlation between PPIs use and not only the increased risk of SBP development but also to other bacterial infections among cirrhotics **[23]**.

Most of the studies linking PPIs use to the development of SBP were retrospective case control studies. **Bajaj and his colleagues** compared 70 SBP patients matched 1:1 for age and CTP class with 70 patients having cirrhosis and ascites. They reported a significantly higher rate of PPIs use in SBP patients (69%) when compared with ascitic cirrhotic patients without SBP (31%) (*P*= 0.0001). On multivariate analysis, PPIs use was independently associated with SBP (*OR*= 4.31), and ascitic fluid protein was protective (*OR*= 0.1) **[20]**. The findings reported in our study were similar to that of **Bajaj et al.** although we investigated a larger cohort of patients.

Furthermore, **Choi et al.** included 176 cirrhotic ascitic patients; 83 SBP patients were compared to 93 controls (without SBP). They concluded that PPIs use (*OR*= 3.443, *P*= 0.025), as well as CTP-class C (*OR*= 2.890, *P*= 0.003) and high MELD scores (≥ 20, *OR*= 3.540, *P*= 0.027) were independent risk factors for SBP development in cirrhotic ascitic patients **[21]**. Moreover, a study done by **Ratelle et al.** compared 51 SBP patients matched 1:2 for age, CTP class and year of admission with 102 comparable cirrhotic patients with ascites who were admitted for conditions other than SBP. The study showed that SBP patients had a significantly higher rate of PPIs use (60.8%) compared with cirrhotic patients without SBP (42.2%) (*P*= 0.03). On multivariate analysis, PPIs use was the only factor independently associated with SBP (*OR*= 2.09) **[22]**.

Several meta-analyses **[24,25,26]** have been conducted and included relevant clinical studies to determine the nature of association of PPIs use and SBP development in cirrhotic patients. Results showed a significant association between the use of PPIs and the development of SBP (*OR*= 2.77) **[24]**; (*OR*= 2.17) **[25]**; (*OR*= 3.15) **[26]**. Furthermore, in 2021, **Alhumaid and his colleagues** conducted a large meta-analysis which aimed at re-assessing the association between PPIs use and SBP development with larger and better-quality data. Twenty three observational (7 case control and 16 cohort) studies were reviewed and 10,386 cirrhotic patients with or without ascites were included in the meta-analysis. The overall results showed a statistically significant association between SBP and PPIs use (*OR*= 1.8). However, the magnitude of the possible association diminished when analysis focused on higher quality data that were more robust. Thus, this updated meta-analysis suggests judicious use of PPIs among cirrhotic patients with ascites **[27].** In agreement with the later conclusion, our study demonstrated that PPIs were used for specified indications, in contrary to many studies **[8,20,22]** which showed that PPIs are sometimes used as an over the counter (OTC) without specified clinical or endoscopic indications.

On the other hand, several studies **[28,29,30,31]** were not in agreement with the result of the current study and they reported no positive correlation between PPIs use and the risk of SBP development. A retrospective case-control study by **Campbell et al.** which included 116 cirrhotic patients with ascites **[28]**; another larger retrospective study done by **Mandorfer et al.** that included 607 consecutive patients with cirrhosis **[29]**; and a retrospective cohort study by **Miozzo and his colleagues** included 258 cirrhotic ascitic patients **[30]** did not confirm the high risk of SBP development among PPIs users. Also, a prospective large study by **Terg et al.** included 23 hospitals in Argentina (enrolled 770 cirrhotic ascitic patients) failed to establish an

association between increased risk of SBP and PPI intake **[31]**.

The current study also examined the indications of PPIs use. The indications for PPIs use in this study were limited to GRED, peptic ulcer disease, post esophageal band ligation or sclerotherapy (Post EBL or EST) and dyspepsia. There was no statistical significant difference between SBP and non-SBP patients as regards indications of use (P >0.05). In-contrast, **Bajaj etal.** and **Goel etal.** reported that cirrhotic patients with SBP have no documented indication for PPIs therapy in 47% and 68% respectively **[20,8]**. Furthermore, results from another study by **Ratelle et al. [22]** showed that about 35% of patients in both SBP cases and control groups had no documented indication for PPIs use which point at PPIs overuse in cirrhotic patients as in previous studies **[32,33]**. This was the rationale to run studies to evaluate the health benefits of depriving decompensated cirrhotic patients from non-indicated use of PPIs **[34]**.

The different generations of PPIs were also focused in the current analysis, and it was obvious that PPIs use among Egyptian patients with cirrhosis and ascites were not limited to certain PPIs, the types used were not statistically different between patients with and without SBP. This looks non-consistent with recommendations from the literature where one systematic review recommended that esomeprazole, omeprazole or rabeprazole to be used in patients with Child class A or B cirrhosis, while only esomeprazole to be used in patients with Child C and all at reduced dose, while pantoprazole and lansoprazole are seen as unsafe among cirrhotics **[35]**. One study showed that pantoprazole and omeprazole were both independently associated with the occurrence of infections including SBP among cirrhotic patients **[36]**.

Limitations of the study include; the small number of patients recruited in each group depending on the high prevalence of cirrhosis in the Egyptian community. Furthermore, several issues related to PPIs use were not investigated including lack of documentation of doses of the used PPIs, compliance with, and end point for PPIs use. In addition, some points are not settled even in the literature for example the total duration of appropriate PPIs use especially post-EVBL/EST. The lack of consensus statement about the timeline that define prolonged use of PPIs beyond which the risks develop is another issue that should be focused in future studies.

CONCLUSION

Among patients with liver cirrhosis and ascites, the rate of PPIs use was higher in SBP patients than in patients without SBP. There were no differences regarding PPIs types or indications of use between both groups. Thus, PPIs therapy should be judiciously used and only when indicated in patients with liver cirrhosis and ascites.

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Conflicts of interest: None.

Ethical considerations

All adult cirrhotic patients who participated in this study gave a written informed consent before being enrolled in the study after explanation for the concept, steps, benefits and risks of the study. The study conforms to declaration of Helsinki. The study was approved by the Institutional Review Board (IRB) of the Faculty of Medicine, Zagazig University.

HIGHLIGHTS

- Spontaneous bacterial peritonitis is a dreading complication in cirrhotic patients with ascites.
- The use of Proton pump inhibitors is associated with development of spontaneous bacterial peritonitis in cirrhotic patients.
- Neither the type of the proton pump inhibitor used nor the indication of its use were associated with the risk of spontaneous bacterial peritonitis development.

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