



FREQUENCY OF SPONTANEOUS BACTERIAL PERITONITIS IN CHRONIC LIVER DISEASE PATIENTS USING PROTON PUMP INHIBITORS.

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ABSTRACT... Objectives: To determine the frequency of spontaneous bacterial peritonitis (SBP) in chronic liver disease patients with ascites using proton pump inhibitors (PPI). **Study Design:** Prospective cohort study. **Setting:** Medicine Unit-II, Shalamar Hospital Lahore. **Period:** From 1st January to 30th June 2017. **Materials & Methods:** A total of 380 patients enrolled in present study were divided into two groups; PPI group and non PPI group. Each group had 190 patients. We performed an extensive matching in both groups to minimize selection bias and SBP incidence was compared in both groups. Multivariate analysis was applied to sort out the causal relationship between PPI use and SBP. **Results:** Applying strict exclusion criteria, SBP incidence in chronic liver disease patients with ascites was found significantly high in PPI group than non-PPI group (12.63% vs. 6.84%, P Value 0.002). Moreover, a large no of patients (39.47%) were using PPI for inappropriate indications while acid peptic disease was the most common indication for its use (60.53%). **Conclusion:** Use of proton pump inhibitors in chronic liver disease patients with ascites significantly increases the risk of spontaneous bacterial peritonitis.

Key words: Spontaneous Bacterial Peritonitis, Chronic Liver Disease, Proton Pump Inhibitors.

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INTRODUCTION

Cirrhosis of liver is a chronic diffuse liver disease characterized by distortion of normal liver architecture and replacement by nodular regeneration and fibrosis. It is widely prevalent in Europe and contributes about 1.5 to 2 % of overall mortality in the region.¹ It ranks 12th among the leading causes of death in the United States, but even this high mortality is still believed to be an underestimation and more research is needed.² One third of the patients with decompensated cirrhosis die within one month and another 30% succumb to death during the first year after onset of infections particularly spontaneous bacterial peritonitis.^{3,4} It is the most frequent and fatal infection in cirrhotic patients and a consequence of frequent alterations in intestinal flora, pathological bacterial translocation and increased intestinal permeability.⁵ Small intestinal bacterial overgrowth (SIBO) and impaired immunity play a vital role in development of bacterial translocation. Invasive procedures such

as paracentesis also contribute to SBP acquired during hospital stay.⁶⁻⁸

Currently, Proton pump inhibitors are one of the most commonly prescribed drugs and are used in a variety of indications such as acid peptic disease, gastro-esophageal reflux disease, Barrett-esophagus, prophylaxis of stress ulcer and NSAID's induced ulcers. As a group, they have been considered to be safe drugs with very few unwanted effects. But over the last decade or so, their antacid action has been extensively studied and various adverse effects have been noted such as increased risk of pneumonia, increased fracture risk, nephrotoxicity, vitamin and mineral deficiencies and increased risk of cardiovascular events.^{9,10}

Gastrointestinal acid acts as a primary defense mechanism against invasion of different microorganisms. Therefore, when Proton pump inhibitors neutralize the acidic environment via

their antacid mechanism, the intestinal flora flourishes relentlessly leading to small intestinal bacterial over growth (SIBO) and hence an increased risk of SBP.¹¹ However, the causal relationship between Proton pump inhibitors and Spontaneous bacterial peritonitis remains to be established.

The rationale of the study is to resolve the variability in the frequency of spontaneous bacterial peritonitis as present in the international published literature. There is no local study till now and findings of this study will be useful for our local population. As stated in the literature that frequency of the disease may change with change in geographical location, so we expect different results in our population. Moreover, the results of this study could be used for future guidelines and patient management plans.

METHODOLOGY

A total of 380 patients with chronic liver disease having ascites were enrolled to assess the frequency of spontaneous bacterial peritonitis. Half of them (190) had previous history of using proton pump inhibitors for more than two weeks while remaining half (190) were without proton pump inhibitors. Confidence interval was taken as 95% with 5% margin of error. Sample size was calculated using WHO formula.

The age range of both male and female patients was 25 to 60 years, having sonographically documented chronic liver disease, paracentesis proven SBP (>250 neutrophils/mm³) and history of PPI use for at least two weeks. Patients excluded from our study were those who had gastrointestinal bleeding with recent drop in hemoglobin of 2 g/dl or more. All the patients with organ transplantation history, those with history of antibiotic use within last 2 weeks and those with tuberculous or carcinomatous peritonitis were also excluded.

The etiology of liver cirrhosis in present study was based on chronic viral hepatitis B, C and alcohol use. Paracentesis was performed under aseptic conditions. Ascitic fluid specimens were inoculated into blood culture bottles and sent for

analysis. Detail history was obtained regarding PPI dosage, duration, indications, adverse effects and patients were evaluated for SBP. All data was collected as per our designed Performa.

All collected data was analyzed using SPSS version 23. Qualitative data like gender, spontaneous bacterial peritonitis, was presented in the form of frequency and percentages. Quantitative data like age (years) was expressed in the form of mean \pm S.D. Data was stratified for type of hepatitis, age, gender and Child-Pugh class to deal with effect modifier. Post stratification chi square test was applied. P-value of 0.05 or less was taken as statistically significant.

RESULTS

In present study, a total of 380 patients were included. All the patients were divided into two groups, PPI group and non PPI group. Number of patients in each group was 190. Male gender was prominent in both groups (58.42% in PPI group and 57.37% in non PPI group) ($p=0.56$). There was no statistically significant difference in mean age of both groups ($p=0.69$). Regarding etiology of chronic liver disease; most of the patients in both groups had chronic hepatitis C infection (51.58% in PPI group and 52.63% in non PPI group) followed by hepatitis B and non-viral alcoholic patients ($p=0.51$) (Table-I).

There was no statistically significant difference in serum albumin, bilirubin, prothrombin time and Child-Pugh scoring of both groups (Table-I). The basic components of Child Pugh score are summarized in Table-II. In terms of PPI use, only 115 (60.52%) patients were using PPI according to standard recommendations. The remaining 75 patients (39.48%) were using PPI for non-specific indications (Figure-1). Among first 115 patients, mostly were using PPI for acid peptic disease (60.86%) followed by GERD (26.08%), esophageal or gastric varices (8.69%) and other indications (4.34%) (Table-III).

Among 190 patients included in PPI group, 18 (9.47%) had at least one episode of SBP during the 6 months of observation, while 6 (3.15%) had two or more than two episodes of SBP. Among

190 patients of non PPI group, only 11 (5.78%) patients had at least one episode of SBP during 6 months while only 2 patients (1.05%) had two

or more than two episodes of SBP (p=0.04) (Figure-2).

Variables	PPI Group (n=190)	Non PPI Group (n= 190)	P-Value
Age (Mean ±SD)	46.90 ± 10.2	47.01 ± 10.1	0.699
Gender			
Male	111 (58.42%)	109 (57.37 %)	0.569
Female	79 (41.58%)	81 (42.63%)	
Etiology of liver disease			
HCV	98 (51.58%)	100 (52.63%)	0.516
HBV	82 (43.16%)	79 (41.58%)	
Alcohol	10 (5.26%)	11 (5.79%)	
Child-Pugh score	8.01 ± 1.7	7.99 ± 1.7	0.78
Albumin	2.8 ± 0.8	2.9 ± 0.7	0.39
Bilirubin	2.9 ± 4.9	2.5±3.99	0.48
Prothrombin time	1.3 ± 0.5	1.3 ± 0.4	0.0038

Table-I. Comparison of baseline characteristics

Parameters	Points Assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Hepatic encephalopathy	None	Grade 1-2	Grade 3-4
Bilirubin, mg/dl	<2	2-3	>3
Albumin, g/dl	>3.5	2.8-3.5	<2.8
Prothombin time (seconds over control)	<4	4-6	>6
INR	<1.7	1.7-2.3	>2.3

CPT classification: Child A: score 5-6 (well compensated); Child B: score 7-9 (significant functional compromise); Child C: score 10-15 (decompensated)

Table-II. Child-Pugh score

Indication for PPI Use	No of Patients (n=115)	Percentage
Acid peptic disease	70	60.86%
GERD	30	26.08%
Esophageal or gastric varices	10	8.69%
Other indications	5	4.34%

Table-III. Indications for PPI use

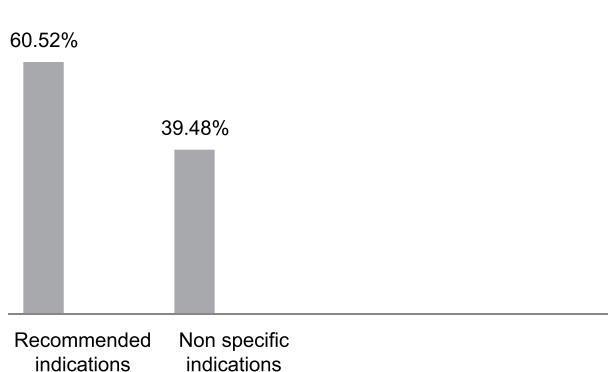


Figure-1. Indications for PPI use according to standard protocols

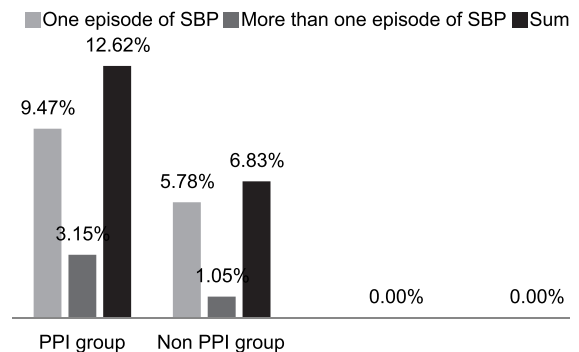


Figure-2. SBP incidence in PPI and non PPI groups

DISCUSSION

Onset of spontaneous bacterial peritonitis in chronic liver disease patients is an alarming sign and carries a high morbidity and mortality in these patients. The major predisposing factor to SBP in these patients is small intestinal bacterial overgrowth.^{12,13} Proton pump inhibitors allow microorganisms to grow within the gastrointestinal tract via its antacid action and neutralization of acidic environment. These microorganisms then lead to SBP in cirrhotic patients.^{14,15}

Majority of the studies conducted on proton pump inhibitors and their role in spontaneous bacterial peritonitis are case control studies which failed to establish a definite causal relationship between the two. Furthermore, study of Campbell and his colleagues raised doubts on this association.¹⁶ Therefore it was necessary to conduct a large cohort study to establish a causal relationship between Proton pump inhibitors and Spontaneous bacterial peritonitis. We performed an extensive matching in both groups to make sure that there is no selection bias and no confounders affect our study results.

Findings of this study showed that incidence of SBP in chronic liver disease patients using PPI were significantly high (two fold) in PPI group as compared to non PPI group (12.62% in PPI group and 6.83% in non PPI group). Regarding more than one episode of SBP, PPI users were having three fold increased risk as compared to non PPI group (3.15% in PPI group and 1.05% in non PPI group). Moreover, an appreciable number of patients (39.48%) were using PPI for inappropriate indications. Most of the patients (60.86%) were using PPI for acid peptic disease. A similar cohort study but with a large sample size was conducted in 2009 which showed that use of Proton pump inhibitors is strongly linked with development of SBP and should only be used where appropriate.¹⁷ Their results were close to our study. In another study, Bajaj and his colleagues noted that frequency of SBP was 69% (almost three fold high risk) among cirrhotic patients who were using PPI.¹⁸ According to a study conducted in Taiwan, incidence of SBP in cirrhotic patients using proton pump inhibitors

was almost two times higher as compared to control group.¹⁹ Another study conducted in Ohio USA showed a statistically significant association between PPI and SBP, but it also emphasized that this association is quantitatively small.²⁰ A meta-analysis carried out in China in 2015 further strengthened the causal relationship of PPI and SBP in chronic liver disease patients.²¹ There were some limitations in the present study. Firstly, PPI dosage was not taken into consideration. It is theoretically possible that high dose PPI may be associated with increased risk of SBP as compared to small dosage.²² Secondly, our study was based on small sample size. In order to establish the causal relationship between PPI and SBP beyond any doubt, large sample sized prospective cohort studies are needed. Thirdly, duration of PPI use in our study was short term (2 weeks), but even this short term use of PPI significantly increased the risk of SBP in our patients. It will be interesting to know in future whether the patients on long term PPI are more prone to SBP or not.

CONCLUSION

Use of proton pump inhibitors in chronic liver disease patients with ascites significantly increases the risk of spontaneous bacterial peritonitis. So, inappropriate use of proton pump inhibitors in chronic liver disease patients should be avoided to minimize the risk of SBP in these patients.

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

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AUTHORSHIP AND CONTRIBUTION DECLARATION

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2	Wali Khan	Manuscript design and review, Literature review.	
3	Sajjad Iqbal	Final review & Proof reading.	