ORIGINAL ARTICLE

Association of Proton Pump Inhibitors with Increased Risk of Spontaneous Bacterial Peritonitis in Patients with Decompensated Chronic Liver Disease: Analytical Cross-Sectional Study

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ABSTRACT

Objective: To look for a possible association between the use of proton pump inhibitors and the development of spontaneous bacterial peritonitis in patients with decompensated chronic liver disease and to draw a comparison between decompensated chronic liver disease patients who are using PPIs and those who are not using them.

Study Design: Analytical cross-sectional study.

Place and Duration of Study: This study was conducted at the Department of Gastroenterology, Combined Military Hospital (CMH), Lahore, Pakistan, from 5th June 2023 to 4th December 2023.

Methods: Patients were divided into two groups. The first group included all patients with decompensated chronic liver disease who were taking PPIs, and the second group included all decompensated chronic liver disease patients who were not taking PPIs at the time of development of Spontaneous bacterial peritonitis. Written informed consent was obtained from all patients in both groups. Inclusion Criteria included patients of the age group ranging from 30 to 80 years having confirmed liver cirrhosis along with splenomegaly and ascites on abdominal ultrasound. Exclusion Criteria included all patients with a history of Child Pugh Class A chronic liver disease, patients with alcohol intake, and patients with gastrointestinal malignancy.

Results: Among diagnosed cases of decompensated chronic liver cirrhosis, the rate of development of spontaneous bacterial peritonitis was 7.58 % in patients using proton pump inhibitors as compared to 1.7 % among patients with chronic liver disease who were not using proton pump inhibitors, with a significant *P*-value of 0.01.

Conclusion: Use of proton pump inhibitors significantly increased the likelihood of developing spontaneous bacterial peritonitis in decompensated chronic liver patients.

Keywords: *Decompensated Chronic Liver Disease, Proton Pump Inhibitors, Spontaneous Bacterial Peritonitis.*

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Introduction

Proton pump inhibitors work by blocking the secretion of gastric acid and therefore are used in many conditions, including the management of long-term dyspepsia, for Helicobacter pylori infection eradication, for the treatment of GERD and Barrett's esophagus, peptic ulcer disease, Upper GI Bleeding, and also along with the use of steroids and NSAIDs for gastric protection.[1] In chronic liver disease patients, the only use of PPIs is to control the bleeding from ulcers that may develop following band ligation of esophageal varices.[2]

In DCLD patients, PPIs are mainly used to control bleeding from severe portal hypertensive gastropathies and after banding of esophageal varices if post-banding ulcers are present.[2] PPIs

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mainly act by acid suppression by blocking the sodium potassium pump. They are used in a variety of other conditions, including non-ulcer dyspepsia, Peptic ulcer disease, GERD, Barrett's esophagus, NSAID-induced gastritis, Zollinger-Ellison syndrome, and for the eradication of H pylori infection.

After their introduction, PPIs largely replaced other antacids due to a better safety profile. They were routinely prescribed by physicians to many patients, even without a specific indication, considering minimal side effects.[3] But over a course of time, several studies conducted showed that they can cause various side effects, such as osteoporosis in post-menopausal women, resulting in fractures sometimes.[4] Similarly, use of PPIs for a long duration can also lead to hospital-acquired pneumonias, it can cause Clostridium Difficile infection, and is associated with increased risk of spontaneous bacterial peritonitis and hepatic encephalopathy in DCLD patients.[5-7]

PPIs were prescribed routinely for a variety of conditions, considering their good safety profile with minimal side effects. They were used in many patients even without any specific conditions, and many physicians still are in the habit of prescribing PPIs to their patients without a clear-cut indication.[3] Over a course of time, many studies conducted showed that the use of PPIs for longer durations is associated with many side effects, such as osteoporosis in post-menopausal women, with increased risk of falls and fractures.[4] Similarly, longer duration use can lead to deficiency of iron, magnesium, and vitamin B12. Some studies even showed they can cause hospital-acquired infections like pneumonias, Clostridium difficile can also occur in intensive care setting even with short-term use of PPIs and spontaneous bacterial peritonitis can also occur in DCLD patients.[5-8]

In DCLD patients, bacterial infection of the ascitic fluid most commonly is caused by spontaneous bacterial peritonitis. It should be taken into consideration in any cirrhotic patient with ascites on clinical examination or confirmed on ultrasound if he or she is febrile and has abdominal pain with or without tenderness.[8] An ascitic fluid sample is withdrawn for routine examination and culture under ultrasound guidance. If it shows a polymorphnuclear leukocyte count of 250 cells/mm3 or more, it confirms that the patient is suffering from spontaneous bacterial peritonitis.[9] If left untreated, SBP has a very bad prognosis with a high mortality rate.[10]

The exact mechanism by which PPIs cause SBP is not clearly understood. There are several possible explanations for the association between PPIs and spontaneous bacterial peritonitis. By suppressing acid secretion in the stomach, PPIs can lead to proliferation of intestinal bacteria, leading to the development of small intestinal bacterial overgrowth (SIBO).[11] These bacteria can colonize the adjacent lymph nodes and can cause infection of the peritoneal fluid in DCLD patients who are already immunocompromised.[12]

Several studies have been conducted, some showing a link between PPIs use and development of SBP, while others don't support this association and are in favor of the use of PPIs in cirrhotic patients.[13,14] But the majority of the studies point towards a possible association between the use of PPIs and the development of SBP in decompensated chronic liver disease patients.[15] To address this conflict, we carried out this analytical cross-sectional study.

The rationale of our study was to correlate PPIs use with increased risk of SBP in DCLD patients who were using PPIs at home and to compare it with those patients who were not using PPIs.

Methods

This analytical cross-sectional study was carried out at the Department of Gastroenterology, Combined Military Hospital (CMH), Lahore, Pakistan, from 5th June 2023 to 4th December 2023. Sample size was calculated with the help of the WHO Sample size calculator (Confidence level 95%, Power = 80, PPI group 3.3 %, Non PPI group 0.7 %).[1] A non-probability consecutive sampling technique was used. A total of 380 patients were included in the study. Approval from the Institutional Ethical Review Committee of the hospital was obtained before the collection and compilation of data vide letter no: 464/2023, dated 21st May 2023. Patients 30 to 80 years of age having confirmed liver cirrhosis with ascites on ultrasound abdomen were included in the study, while patients with a history of alcohol intake, gastrointestinal malignancy, and compensated liver disease were

excluded. All patients included in the study were distributed into group A and B as per their history of intake of PPIs at home, with a mean duration of use of PPIs for 6 months, and good compliance was considered. All patients were using Omeprazole 20-40mg daily. Group A was assigned to individuals using PPIs, while others were allocated to Group B. Patients' contact numbers were obtained, and all collected data were entered in the data collection form. Both Mean and standard deviation was calculated for quantitative variables like age. The categorical or qualitative variables, like gender, use of PPI, and development of SBP, were all presented in terms of percentages and frequencies. All collected data were analyzed using Statistical Package for Social Sciences (SPSS) version 14. Both groups were compared for all outcomes mentioned before. *P*-value ≤ 0.05 was considered statistically significant

Results

A total of 380 patients diagnosed with cases of decompensated cirrhosis were studied and were divided into two groups. Group A included patients using PPIs (N= 211) while Group B included patients with decompensated cirrhosis who were not using PPIs (N= 169). The age distribution ranged from 43 to 88 years in the study. Minimum age was 43 years (N=6) and maximum age was 88 years (N=12) with a mean age of 65.08 ± 11.3 (Figure 1).

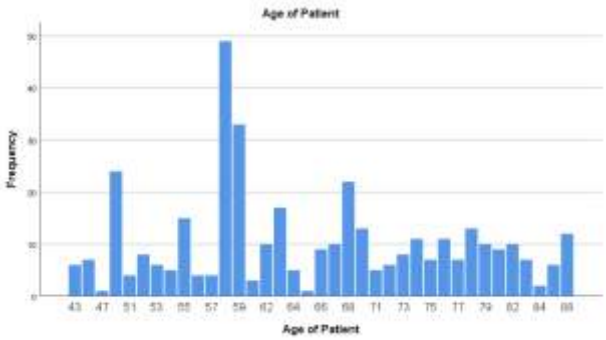

Fig.1: Age Distribution

Mean age in Group A was 64.36 ± 11.48, while mean age in Group B was 65.99 ± 11.02 (*P*-value 0.163). Among the 380 patients studied, 203 were males (53.4%) and 177 were females (46.6%). Among the 211 patients in Group A, 92 were males (43.6 %) and 119 were females (56.4 %). Group B included 111 males (65.7%) and 58 females (34.3%). Among 203 male patients, 7 males (3.4 %) developed Spontaneous bacterial peritonitis, while among 177 females, 12 (6.7 %) developed Spontaneous bacterial peritonitis (*P* value < 0.001) (Table 1).

A total of 16 patients (7.58 %) in Group A developed SBP, while in Group B, 3 patients (1.7 %) developed Spontaneous bacterial peritonitis. The groups had a statistically significant difference in the frequency of development of Spontaneous bacterial peritonitis, with a Chi-Square *P*-value of 0.009 (Table 2).

Among 211 individuals using PPIs, 101 (47.8 %) experienced variceal bleeding, while in the other group, who were not using PPIs, variceal bleeding occurred in 74 individuals out of 169 (43.7 %). These values showed an insignificant correlation (*P* value = 0.428). Among 175 patients experiencing variceal bleeding, only 9 (5.1 %) developed Spontaneous bacterial peritonitis, while 10 (4.8 %) patients developed Spontaneous bacterial peritonitis among 205 patients who did not have variceal bleeding (*P* value = 0.906) (Table 3).

Severity of disease (Child-Pugh class) was also studied and correlated with the incidence of spontaneous bacterial peritonitis. Among 279 individuals belonging to Child class B, 13 (4.6 %) developed Spontaneous bacterial peritonitis. However, among 101 individuals belonging to Child class C, 6 (5.9 %) developed Spontaneous bacterial peritonitis. The correlation between disease severity and the incidence of Spontaneous bacterial peritonitis remained insignificant (*P* = 0.613). (Table 4).

Table 1: Comparison of groups in terms of Gender

Gender	Group A N (%)	Group B N (%)	Total	*Chi-Square* test	*P*-Value
Male	92 (43.6)	111 (65.7)	203	18.36	<0.001
Female	119 (56.4)	58 (34.3)	177		
Total	211	169	380		

Table 2: Comparison of Groups in terms of Spontaneous bacterial peritonitis

Spontaneous bacterial peritonitis	Group A N (%)	Group B N (%)	Total	*Chi Square* test	*P*-Value
Yes	16 (7.58)	3 (1.7)	19		
No	195 (92.42)	166 (98.3)	361	6.66	0.009
Total	211	169	380		

Table 3: Comparison of Variceal bleeding in terms of Spontaneous bacterial peritonitis

Spontaneous bacterial peritonitis	Variceal bleeding		Total	*Chi Square* test	*P*-Value
	Yes N (%)	No N (%)			
Yes	9 (5.1)	10 (4.8)	19		
No	166 (94.9)	195 (95.2)	361	0.014	0.906
Total	175	205	380		

Table 4: Comparison of Severity in terms of Spontaneous bacterial peritonitis

Spontaneous bacterial peritonitis	Severity		Total	*Chi Square* test	*P*-Value
	Child Class B N (%)	Child Class C N (%)			
Yes	13 (4.6)	6 (5.9)	19		
No	266 (95.6)	95 (94.1)	361	0.26	0.613
Total	279	101	380		

Discussion

A lot of studies have been conducted regarding the association of PPIs use and the development of SBP in DCLD patients, but the results are conflicting. Some studies show there is a strong association, while others deny it. Campbell et al. in 2008 in a case control study showed no association between PPIs use and Spontaneous bacterial peritonitis development.[13] Similarly, a retrospective study done by Mandorfer M et al. also did not show any link between use of PPIs and development of SBP, which included 607 cirrhotic patients.[16] A large prospective study comprising 770 cirrhotic patients done by Terg et al. in Argentina also revealed there is no role of use of PPIs in causing Spontaneous bacterial peritonitis development.[17] A study conducted in Korea on 307 cirrhotic patients to compare the effects of PPIs on the development of SBP in patients using PPIs and those who are not using them, found that there was no difference between the two groups.[18]

On the other hand, there are many studies that support the link between use of PPIs and SBP development. One meta-analysis done in 2011, comprising four different studies on 772 patients, showed a strong link between PPIs use and Spontaneous bacterial peritonitis development.[15] Another study done in 2013 on cirrhotic patients to see for a possible link between use of PPIs and SBP development compared patients taking PPIs to those taking H2 receptor blockers and found that those using PPIs were at increased risk for development of Spontaneous bacterial peritonitis.[19] Another meta-analysis comprising 12 studies conducted between 2008 and 2014 involving more than 8000 patients also showed a strong association between use of PPIs and development of SBP in cirrhotic patients.[20] More recently, the largest meta-analysis conducted in 2021, comprising 23 studies and including more than 10,000 patients, also showed a strong link between use of PPIs and development of Spontaneous bacterial peritonitis in DCLD patients.[21]

Due to the conflict between various studies and meta-analyses, we conducted this analytical cross-sectional analysis of data collected from decompensated chronic liver disease patients by dividing them into two groups. One group was using PPIs at home, and the other group was not taking PPIs. Our analysis showed that use of PPIs in DCLD patients is strongly linked with the occurrence of SBP, and those taking PPIs are at increased risk as

compared to those who are not using them.

In decompensated chronic liver disease patients, PPIs are indicated only after endoscopic band ligation of varices to control bleeding ulcers, and that too for a limited time. Similarly, to control bleeding complications of severe portal hypertensive gastropathies. The aim of the study is to make physicians aware of this thing and to avoid inappropriate use of PPIs for a long duration without any indication, especially in cirrhotic patients. Similarly, PPIs used for the purpose of prophylaxis in cirrhotic patients to control peptic complications is also not advisable as acid secretion is already suppressed in liver cirrhosis.[22]

Cirrhotic patients are already immunocompromised and use of PPIs causes increase in bacterial colonization and can contribute to bacterial infection of the ascetic fluid causing SBP.[1] Sipeki N et al. in a study showed that some sort of immune dysfunction syndrome occurs in cirrhotic patients.[23] In another study, it was shown that administration of omeprazole is associated with inhibition of in vitro human neutrophil phagocytosis and acidification of phagolysosome.[24] A study conducted by Garcia-Martinez I et al. revealed that cirrhotic patients exposed to PPIs showed a considerable decrease in granulocyte and monocyte cellular oxidative burst, ultimately resulting in decreased immunity in these patients and increased risk of bacterial infections.[25]

Some studies suggest that there might be some other mechanisms by which the use of PPIs is linked with the increased risk of occurrence of SBP. One study showed that even short-term use of PPIs is associated with increased risk as compared to long-term use.[26] But SIBO cannot develop in a short time, so additional mechanisms need to be looked at to show how this can happen.

Our study did not take into consideration the history of spontaneous bacterial peritonitis in the past, which is a risk factor for further SBP development. Therefore, further studies are required to exactly correlate the link between the use of PPIs and the occurrence of spontaneous bacterial peritonitis in DCLD patients.

Conclusion

To conclude, our analytical cross-sectional study showed that use of PPIs is a strong risk factor for the occurrence of SBP in DCLD patients, and those patients who are taking PPIs regularly are at increased risk of having this life-threatening condition as compared to those decompensated liver disease patients who are not using PPIs. We recommend the judicious use of PPIs in DCLD patients only for the specified indications mentioned above and for a specified duration. However, further studies are needed to further establish this association.

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Author Contributions

AH: Conception and design of the work
RU: Writing the original draft, proofreading, and approval for final submission
RK: Manuscript writing for methodology design and investigation
MAM: Data acquisition, curation, and statistical analysis
AM: Validation of data, interpretation, and write-up of results
SA: Revising, editing, and supervising for intellectual content