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Original Article

Association Between Proton Pump Inhibitors (PPI) use and Spontaneous Bacterial Peritonitis (SBP) in patients of Cirrhosis with Sepsis

Raja M Waqar Khan, Shazia Nisar, Kamran Ali

Department of General Medicine, Pak Emirates Military Hospital/National University of Medical Sciences (NUMS), Rawalpindi Pakistan

ABSTRACT

Objective: To find the relationship between Proton Pump Inhibitors (PPIs) use and development of Spontaneous Bacterial Peritonitis (SBP) in patients of cirrhosis with sepsis.

Study Design: Comparative cross-sectional study.

Place and Duration of Study: Medicine Department, Pak Emirate Military Hospital, Rawalpindi Pakistan, from Apr 2020 to May 2021.

Methodology: The patients enrolled were classified as proton pump inhibitor users (Group-A) and non-users (Group-B). The clinical diagnosis of cirrhosis was established by combination of history, examination, laboratory, ultrasound, upper GI endoscopy and by fibro-scan. They were observed and evaluated during the admission for spontaneous bacterial peritonitis and other infections. Chi-square test was used to check for association between variables.

Results: Total number of patients who participated in this study were 103, out of which 53(51.5%) were proton pump inhibitor (PPI) users and 50(48.5%) were non-PPI users. There was an increased chance of bacterial infection among Group-A (38%) than Group-B (p=0.001). Statistically significant difference was also noted for spontaneous bacterial peritonitis (p=0.049) across groups.

Conclusion: Proton pump inhibitor use increased the risk for development of spontaneous bacterial peritonitis in patients of cirrhosis who also had sepsis. Therefore, it is better to avoid proton pump inhibitors in cirrhosis patients with sepsis.

Keywords: Cirrhosis, Peritoneum, Proton Pump Inhibitor, Sepsis, Spontaneous Bacterial Peritonitis.

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INTRODUCTION

The chief function of proton pump inhibitors (PPIs) is to reduce acid production in stomach.[1] Spontaneous Bacterial Peritonitis (SBP) occurs when peritoneum become inflamed secondary to infection that occur in fluid that is accumulated in peritoneal cavity, which can lead to sepsis.[2,3]

In patients with cirrhosis, the accumulation of certain proteins in the abdominal cavity occurs due to over production of bacteria and these proteins hold the fluid which is called the ascetic fluid.[4] When there is bacterial contamination of ascetic fluid it causes spontaneous bacterial peritonitis and because in the gastrointestinal tract PPI use creates favorable medium for bacteria to overgrow, which can invade the ascetic fluid and contaminate it causing SBP.[5,6]

The likely linkage between PPIs use and increase incidence of SBP in patients of liver cirrhosis with sepsis is a subject need to be studied in detail.[7] Miozzo *et al.*, found that there was no difference in incidence of SBP in patients with and without use of proton pump inhibitors.[8] A study performed in patients of cirrhosis from Qatar concluded that increasing age and use of PPIs was associated with SBP, and other infections in study partiicpants.[9]

A recent local study revealed that patients suffering from cirrhosis with ascites, consuming PPIs were more likely to develop SBP as compared to non-PPI users.[10] Limited local data had been available in this regard. We therefore designed this study with the rationale to find out relationship between PPIs use and development of SBP in patients of cirrhosis with sepsis.

METHODOLOGY

This comparative cross-sectional study was conducted at the Medicine Department of Pak Emirates Military Hospital, Rawalpindi Pakistan from April 2020 to May 2021. Ethical approval was obtained via letter no A/28/EC/282/2021.

Inclusion Criteria: Patients of either gender aged between 18 and 60 years with cirrhosis, admitted to inpatient medical department or intensive care unit with acute complications of cirrhosis such as variceal

Correspondence: Dr Raja M Waqar Khan, Department of General Medicine, Pak Emirates Military Hospital, Rawalpindi Pakistan
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bleeding, hepatic encephalopathy, hepato-renal syndrome, refractory ascites and diagnosis of hepatocellular carcinoma diagnosis for the first time were included.

Exclusion Criteria: Patients using steroids or having any medical or immunological condition other than cirrhosis making them immunocompromised, and those with any known allergy to PPIs were excluded.

Non probability consecutive sampling was used to recruit patients for the study. Sample size was calculated using WHO sample size calculator taking population prevalence proportion of SBP in patients of cirrhosis as 46%.[11]

To check acid suppressive medication intake, treatment charts were reviewed for acid suppressive medication use and patients were categorized as PPI users (Group-A) versus non-PPI users (Group-B). The PPIs used were either pure or its derivative containing Omeprazole, Esomeprazole, Lansoprazole, Rabeprazole or Pantoprazole. Cirrhosis of liver was diagnosed by fibro-scan, liver biopsy or cumulative findings on history, examination, laboratory, ultrasound and endoscopic findings. The decision to perform liver biopsy was made in each case depending upon various factors like diagnostic requirement as well as patient's preference and willingness. Standard criteria was used to establish presence of infection, i.e., (1) SBP: Polymorphonuclear cells >250 cells/mm3 in ascitic fluid; (2) spontaneous bacteremia: positive blood culture for microbes without a known focus; (3) Chest infection: presence of fresh infiltrate or consolidation (a) At least one respiratory symptom (cough with sputum, difficulty in breathing, chest pain) with (b) minimum one finding on auscultation of chest i.e crepitations or bronchial breathing along with minimum 2 of the following: (a) temperature rise of greater than 38°C or less than 36°C, (b) pulse rate greater than 90 beats per minute at rest and respiratory rate above 20 per minute, and rigors and chills or WBC >10,000/mm3 or <4,000/mm3) without use of antibiotics; and UTI along with white blood cell >15/HPF with positive gram stain or culture of urine.[12-14]

Statistical Package for Social Sciences (SPSS version 24) was used for analyzing data. Statistical Analysis used for categorical variables were expressed expressed as frequencies and percentages and for continuous variables Mean±SD (standard deviation) was used. For establishing association between the variables, Chi-square analysis and Fischer Exact tests were used.A *p*-value less than or equal to 0.05 was considered statistically significant.

RESULTS

Total patients included in the study were 103, out of which 80(78.1%) were male. Chronic HCV infection 46(44.6%) and chronic HBV infection 22(21%) were the leading causes of cirrhosis. Among them spontaneous bacterial peritonitis was present in 19(18.4%) patients. Table-I summarizes the basic characteristics of patients in both groups. Out of 103 patients 53(51.4%) patients were using proton pump inhibitors (Group-A) and 50(48.6%) were not using proton pump inhibitors (Group-B).

Table-I: Basic Characteristics of Patients (n=103)

Study parameters	Group-A	Group-B
Demographics		
Age (years) Mean±SD	55.3±11.7	50.2±11.8
Males	39(73.6%)	41(82.0%)
Comorbidities		
Smoker	17(32.2%)	14(29.6%)
Diabetes mellitus	29(55.0%)	18(36.4%)
Hypertension	20(38.6%)	11(21.6%)
Chronic kidney disease	20(5.3%)	1(1.9%)
Etiology of Cirrhosis		
Chronic hepatitis B	12(22.6%)	10(20.0%)
Chronic hepatitis C	25(47.1%)	21(42.0%)
Alcoholic liver disease	2(3.7%)	3(6.0%)
Autoimmune hepatitis	2(2.9%)	1(1.9%)
Primary biliary cirrhosis	1(1.8%)	1(1.9%)
Cardiac cirrhosis	1(0.6%)	0(0%)
Cryptogenic cirrhosis	11(22.2%)	9(17.9%)
Other causes	2(2.9%)	2(4.3%)
Child-Pugh score		
A	19(37.4%)	22(43.8%)
B	20(38.0%)	17(34.6%)
C	13(24.6%)	11(21.6%)

Table-II: Infection Rates across Groups (n=103)

	Group-A n(%)	Group-B n(%)	*p*-value
Spontaneous bacterial peritonitis	13(25.7%)	5(10.5%)	0.049
Respiratory infection	3(5.3%)	1(1.5%)	0.325
Urinary tract infection	1(0.6%)	1(1.5%)	0.0.967
Septic shock	3(6.4%)	1(1.5%)	0.325
Sum of infections	20(38%)	8(16%)	0.001

Table-II summarizes the results of statistical analysis. Patients in Group-A had a comparatively higher incidence of bacterial infection as compared to Group-B patients (p=0.001). Statistically significant difference was also noted for spontaneous bacterial peritonitis (p=0.049) among proton pump inhibitor users and non-users. There was no significant difference in the frequency of urinary tract infections,

respiratory tract infections and septic shock across groups (p>0.05).

DISCUSSION

This study emphasized the fact that proton pump inhibitors (PPIs) use in patients with cirrhosis of the liver increased the probability of infection and spontaneous bacterial peritonitis (SBP) development, which indicates the linkage between proton pump inhibitor use and spontaneous bacterial peritonitis. PPIs are commonly used in medical practice. Previously, many studies showed their adverse effects.[5] Use of PPIs in patients with cirrhosis weakens immunity, which negatively impacts an already compromised immune system.[6,7] There is still a debate on whether or not PPI use is linked with increased incidence of SBP in cirrhotic patients with sepsis. We conducted this study with the aim to find out the relationship between PPI use and development of SBP in patients of cirrhosis with sepsis.

Our study, which included 103 cirrhotic patients, supported the argument that the use of proton pump inhibitors was linked with the development of spontaneous bacterial peritonitis in these patients.[14] Similar results have been published by Cole *et al.*, in 2016.[15] Necessary precautions should be required to implement that PPIs should only be used in cirrhotic patients when the proposed benefit is more as compare to adverse effects.

Janka *et al.*, in 2020, published a study which concluded that long-term PPI use was associated with the development of SBP and a progressive disease course in patients with cirrhosis.[16] Our results were not very different from them as overall infection rate and spontaneous bacterial peritonitis was seen more in patients of cirrhosis who were using proton pump inhibitors as compared to those who were not using these medications.

A study published in India in 2018 assessed the effects of PPIs in patients being managed for cirrhosis of the liver.[17] It was concluded that risk of SBP was doubled in patients who used PPIs. However, use of beta blockers was associated with risk lowering of SBP in these patients. We did not study any other medications but regarding use of PPIs, our results were similar to Rajender *et al.*[17]

Min *et al.*, in their study, concluded that proton pump inhibitor use significantly increased the risk of spontaneous bacterial peritonitis in 1965 patients with cirrhosis and ascites.[18] They recommended use of these medications with caution in these patients. Our results also revealed that proton pump inhibitor use increased the risk for development of spontaneous bacterial peritonitis in patients of cirrhosis who also had sepsis. Therefore, it is better to avoid proton pump inhibitors in cirrhosis patients who have sepsis.

LIMITATION OF STUDY

Multiple factors could lead to SBP and other infections in patients suffering from liver cirrhosis and with this study design we could not establish that use of PPIs was cause of SBP in these patients. Studies with better design and sample from multiple medical and GI units may generate results which could be generalized and used in making guidelines regarding use of PPIs in these patients.

CONCLUSION

Proton pump inhibitor use increased the risk for development of spontaneous bacterial peritonitis in patients of cirrhosis who also had sepsis.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

RMWK & SN: Data acquisition, data analysis, critical review, approval of the final version to be published.

KA: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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