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ASSOCIATION BETWEEN PRE HOSPITAL USE OF PROTON PUMP INHIBITORS AND SPONTANEOUS BACTERIAL PERITONITIS IN PATIENTS PRESENTING WITH LIVER CIRRHOSIS.

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ABSTRACT… Objectives: To determine the association between pre hospital use of proton pump inhibitors and spontaneous bacterial peritonitis in patients presenting with liver cirrhosis. **Study Design:** Case control study. **Setting:** Department of Gastroenterology at Liaquat National Hospital Karachi. **Period:** Six months (From March-2017 to August-2017). **Material and Methods:** There were 120 patients with cirrhosis were included in this study. Sixty patients were cases with spontaneous bacterial peritonitis (SBP) and 60 patients were control without spontaneous bacterial peritonitis. All patients were interviewed for pre hospital intake of PPI (as per operational definition). All the data was entered on predesigned proforma (attached). **Results:** The average age of the patients was 42.47±9.87 years. Rate of PPI use was significantly higher among cases with SBP (46.7%) as compared to the patients without SBP (23.3%). **Conclusion:** In conclusion, PPI use (acid suppression) was associated with the development of SBP in cirrhotic patients with ascites. We recommend that PPI indications in cirrhotic patients should be frequently re-evaluated with particular attention devoted to duration of use, especially following endoscopic variceal ligation (EVL).

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

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INTRODUCTION

The cirrhotic patients are more prone to acquire bacterial infections due to immunocompromised and the common infections detected are spontaneous bacterial peritonitis (SBP) pneumonia and urinary tract infections.[1,2] Liver cirrhosis responsible for increase mortality and morbidity by various complications as ascites, hepatic encephalopathy, esophageal varices, hepatoma and hepatopulmonary and hepatorenal syndrome.[3,4] The patients with liver cirrhosis shown higher susceptibility to various microorganisms due to impaired in immune system. Among them the spontaneous bacterial peritonitis is the common and frequently observed complication but its prevalence is decreasing due to a timely diagnosis and early initiation of specific treatment.[5,6] SBP is defined as paracentesis yielding ≥250 polymorphonuclear leucocytes/ml.[7] Bajaj, et al observed individuals with SBP had a significantly higher rate of pre-hospital proton-pump inhibitors (PPIs) use (69%) compared with cirrhotics with ascetes hospitalized without SBP (31%). PPI use was independently associated with SBP[8], and de Vos M et al, also reported that PPI usage participants have hgher chance for SBP (49%) than without SBP (25%).[9] Miura K et al., also reported PPI usage and SBP as 88.9% than without SBP as 57.4%.[10]

Rationale of this study was to compare the frequency of pre-hospital use of proton pump inhibitors with & without SBP in subjects with liver cirrhosis. Proton pump inhibitors (PPIs) impair gastric secretion, favors bacterial growth in upper GIT, delayed gastric emptying leads to bacterial overgrowth. There is no local literature available upon which we can suppress the use of PPIs. So through this study we want to prove that PPI use in cirrhotic patients may develop SBP. Through this study we was able to know the association of PPI with SBP in cirrhotic patients and if found

any significant association between the two then a department protocol was found to prevent such a common complication of this morbidly disease by restricting the PPI prescriptions without indications.

PATIENTS AND METHODS

This six months case control study was conducted (From 1st – March-2017 to 31st – August-2017) in department of Gastroenterology, Liaquat National Hospital Karachi.

Inclusion Criteria

- Patients of either gender, aged 25-60 years admitted with cirrhosis (as defined in operational definition), for >6 months Child-Pugh score A, B, C.
- **Cases:** patients with SBP
- **Controls:** patients without SBP

Exclusion Criteria

- The individuals on antibiotic prophylaxis or with gastrointestinal bleeding.
- Patients with secondary bacterial peritonitis, peritoneal tuberculosis or peritoneal carcinometosis (on medical record and clinical examination).

Cirrhosis of Liver

Presence of any three or more of the following clinical signs and symptoms: anorexia, fatigue, weakness, weight loss (>5kg), jaundice (yellow skin and eyes) and confirmed on ultrasonography showing all three of the following: nodularity, irregularity and increased echogenicity of the liver.

Spontaneous Bacterial Peritonitis

It is defined as presence of ascitic PMN count >250cells x mL on endoscopy in absence of an intraabdominal source of infection.

Proton Pump Inhibitors (PPI) Use

It was labeled as history of use of prehospital acid-suppressive therapy like PPI up to 40mg/24hrs for >2 weeks.

One hundred 20 patients fulfilled the selection criteria was enrolled in the study Informed consent was obtained & demographic details like name, age, gender, contact was obtained. Then patients were divided in two groups on the basis of presence or absence of SBP. All patients were interviewed for prehospital intake of PPI. All the data was entered on predesigned proforma (attached).

The data was analyzed on SPSS version 17.0. Independent sample t-test was use to compare means. The frequency and percentage was while chi-square test was used for statistical significance with level of significance was $P \leq 0.05$.

RESULTS

There were 120 patients with cirrhosis included in this study. Sixty patients were cases with spontaneous bacterial peritonitis (SBP) and 60 patients were control without spontaneous bacterial peritonitis. The average age of the patients was 42.47±9.87 years. Mean age and duration of disease was not significant between groups as shown in table 6. Out of 120 patients, 66(55%) were male and 54(45%) were female.

Rate of PPI use was significantly higher among cases with SBP (46.7%) as compared to the patients without SBP (23.3%). Use of PPI was three times more likely in patients with SBP than without SBP [OR= 2.87; 95%CI 1.31-6.29].

Regarding type of PPI, esmoprazol was used in 50% (21/42) cases, omiprazol used in 38.1% (16/42) and rabeprazolany used in 11.9% (5/42) cases. Stratification analysis was performed and observed that rate of PPI used was not significant between groups for below and equal to 40 years and above 40 years of age.

Rate of PPI Use was high in SBP group for male and female but it was only statistically significant for male cases and not significant for female cases. Similarly rate of use of PPI was observed with respect to duration of disease (≤12, >12). The results are presented in Figure 1-2 and Table-I-VI.

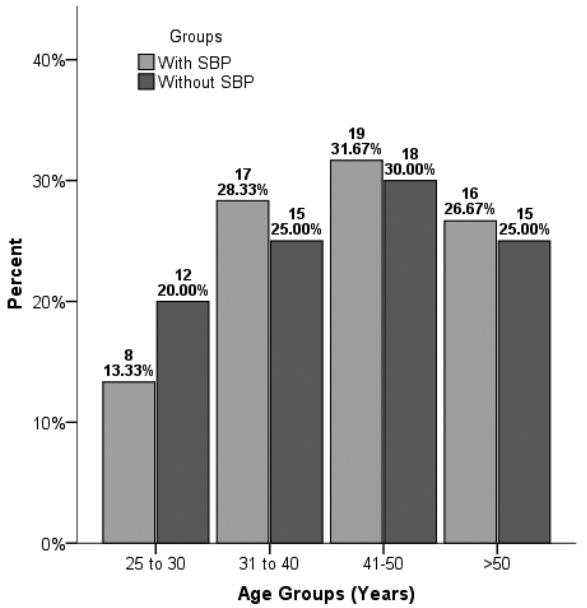

Figure-1. Age with respect to groups n= 120

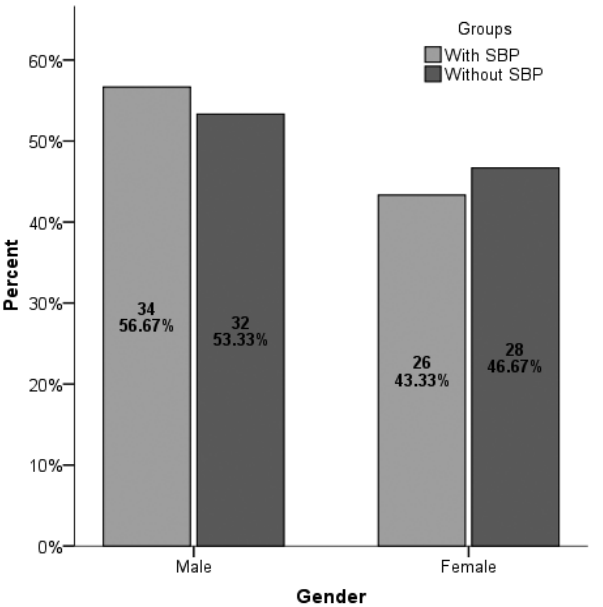

Figure-2. Gender with respect to groups n= 120

PPI	The Subjects with SBP n=60	The subjects without SBP n=60	P-Value	OR[95%CI]
Used	28(46.7%)	14(23.3%)	0.007	2.87 [1.31-6.29]
Not Used	32(53.3%)	46(76.7%)		
Chi-Square test applied * significant OR= odd ratio = 28x46 / 14x32				

Table-I. The association between PPI and SBP

PPI	The Subjects With SBP n=28	The Subjects Without SBP n=14	Total n=42
Omiprazol	8(28.6%)	8(57.1%)	16(38.1%)
Esmoprazol	17(60.7%)	4(28.6%)	21(50%)
Rabeprazolany	3(10.7%)	2(14.3%)	5(11.9%)

Table-II. Type of PPI according to groups n=42

PPI	The Subjects with SBP n=25	The Subjects Without SBP n=27	P-Value	OR[95%CI]
Used	12	6	0.51	3.21 [0.97-10.72
Not Used	13	21		
Chi-Square test applied * significant OR= odd ratio				

Table-III. Association between use of PPI and SBP in accordance to age ≤40 years

PPI	The Subjects with SBP n=35	The Subjects Without SBP n=33	P-Value	OR[95%CI]
Used	16(45.7%)	8(24.2%)	0.64	2.63 [0.93-7.42]
Not Used	19(54.3%)	25(75.8%)		
Chi-Square test applied * significant OR= odd ratio				

Table-IV. Association between use of PPI and SBP in accordance to age >40 years

PPI	The Subjects with SBP n=34	The Subjects Without SBP n=32	P-Value	OR[95%CI]
Used	14(41.2%)	6(18.8%)	0.048	3.03 [0.99-9.29
Not Used	20(58.8%)	26(81.3%)		
Chi-Square test applied * significant OR= odd ratio				

Table-V. Association between use of PPI and SBP for male gender

PPI	The Subjects with SBP n=26	The Subjects Without SBP n=28	P-Value	OR[95%CI]
Used	14(53.8%)	8(28.6%)	0.096	2.91 [0.94-8.98]
Not Used	12(46.2%)	20(71.4%)		
Chi-Square test applied * significant OR= odd ratio				

Table-VI. Association between use of PPI and SBP for female gender

DISCUSSION

SBP have bad prognosis and acid suppression by H2 blockers and PPIs have been widely used for gastric discomfort and pain because of their good efficacy and symptomatic relief.[11] Acid suppressants exert their effects by reducing gastric acid in the stomach.[12] The alteration in gastric pH can change the normal gastrointestinal flora and vulnerable to infection by various pathogens.[13-15]

In current series, there were 120 patients with cirrhosis were included in this study. Sixty patients were cases with spontaneous bacterial peritonitis (SBP) and 60 patients were control without spontaneous bacterial peritonitis. The average age of the patients was 42.47±9.87 years. Out of 120 patients, 66 (55%) were male and 54 (45%) were female and this male predominance is supported by former study.[16]

The results of the current study support an association between PPI use and the development of SBP in cirrhotic patients with ascites. We found that Rate of PPI use was significantly higher among cases with SBP (46.7%) as compared to the patients without SBP (23.3%). Use of PPI was three times more likely in patients with SBP than without SBP [OR= 2.87; 95%CI 1.31-6.29].[17] In 2009, Bajaj et al[8] performed a retrospective case-control study involving 70 patients with SBP & observed that PPI use was associated with SBP while Choi, et al[17] also reported PPI usage and risk of SBP. In contrast there was no difference in PPI usage with and without SBP in former studies.[7,18]

Thus we recommended that PPI indications in cirrhotic patients should be frequently re-evaluated with particular attention devoted to duration of use, especially following Endoscopic variceal ligation (EVL). The minimal effective PPI dose should be used in advanced cirrhosis because it is known that PPI exposure is increased in these patients because of an altered pharmacokinetic profile. The double-standard dose should also be avoided whenever possible. Proton pump inhibitors (PPIs) might be hazard factor for hepatic encephalopathy (HE) in individuals with liver cirrhosis, conceivably through translocation of gut microscopic organisms which can likewise prompt spontaneous bacterial peritonitis (SBP).[19] PPI usage and age (> 40 years) are risk factors for SBP in hospitalized cirrhotic population. Except if it is demonstrated, PPI treatment should be avoided in cirrhotic population especially in advance age group.[20]

CONCLUSION

PPI use (acid suppression) leads to occurrence of SBP in cirrhotic population with ascites. Therefore large advance multi-centered studies are required in urban as well as rural populated hospitals to evaluate and prove the association between PPI and risk of SBP.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	M. Hussain Baloch	Contributions to conception and design, acquisition of data, analysis and interpretation of data.	
2	Riaz Hussain Awan	Drafting the article and shares ites expert research opinion and experience in finalizing the manuscipt.	
3	Seema Nayab	Contributed in conception and interpretation of data and give his expert view for manuscript designing.	
4	Khadim Hussain Awan	Collection and acquisition of data, analysis and interpretation of data and make it suitable for final revision and a corresponding author.	
5	Faqir Muhammad Awan	Data collection and analysis.