

## Original Research Article

# Proton pump inhibitor: a risk factor for spontaneous bacterial peritonitis in Indian cirrhotics decompensated with ascites

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**Received:** 15 November 2018

**Accepted:** 29 December 2018

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## ABSTRACT

**Background:** Spontaneous bacterial peritonitis (SBP) is common complication of cirrhosis caused by bacterial translocation. Bacterial colonization and overgrowth may occur in GI tract on suppression of gastric acid secretion. Beta-blockers have been postulated to reduce intestinal permeability. There is no significant Indian study to evaluate association of PPI with SBP in cirrhotic ascites. We aimed to assess the effect of PPI in cirrhotic patients decompensated with ascites.

**Methods:** A retrospective case control study (January 2016 to April 2018), evaluated subjects with cirrhosis and ascites. Two study groups of cirrhotic subjects with and without SBP were formed. In each of the two study groups, 143 subjects, were enrolled by matching for age, year of admission, Child-Pugh-Turcotte (CTP) class after considering the inclusion and exclusion criteria. PPI use and various other correlates were compared in both study groups. SPSS ver 24.0 was used for statistical analysis.

**Results:** About 69.23% subjects were using PPI prior to admission in SBP group, which was significant compared to only 31.47% in cirrhotics without SBP (p 0.003). On multivariate analysis PPI use was an independent risk factor for SBP (OR 2.24, 95% CI: 1.01-4.24; p value 0.033) and beta blocker use was protective (OR 0.58; 95% CI: 0.4-0.8; p 0.001).

**Conclusions:** PPI use doubles the risk of development of SBP in cirrhotics decompensated with ascites. In contrast, Beta blockers use significantly lowers the risk of SBP.

**Keywords:** Ascites, Cirrhosis, PPI, SBP

## INTRODUCTION

Spontaneous bacterial peritonitis (SBP) is a common complication in patients with cirrhosis, and is associated with poor long term prognosis and significant mortality.<sup>1,2</sup> SBP is believed to result from translocation of bacteria across the intestinal wall, owing to increased gut permeability and small intestinal bacterial overgrowth.<sup>3,4</sup> Owing to impaired phagocytic activity by reticulo-endothelial system, neutrophil dysfunction and

complement deficiency, cirrhotics are more susceptible to infections.<sup>5-7</sup> Acidic gastric secretions act like a defense mechanism against ingested microorganism. Proton pump inhibitors has been associated with an increased susceptibility to enteric infections caused by various enteropathogens including *Salmonella*, *Campylobacter* and *Clostridium difficile*.<sup>8,9</sup> Such enteric bacteria may translocate from gut in portal hypertensive milieu.<sup>4,8</sup> Overuse of PPIs have been reported in cirrhotics.<sup>9</sup> PPI metabolism in Indian population is different owing to

prevalent common allelic polymorphisms. CYP2C19\*2 is the most common allele occurring at a higher frequency of 41%, when compared to African Americans (25%) and Asian populations (28-30.3%).<sup>10-13</sup> A diminished enzyme activity, altered pharmacokinetics, higher plasma levels of PPI, more potential adverse events makes Indians cirrhotics a unique subpopulation to study. We aimed to evaluate whether PPI use in Indian subjects with cirrhotic ascites was associated with spontaneous bacterial peritonitis (SBP).

## METHODS

In a retrospective case-control observational study, we evaluated records from January 2016 to April 2018, for patients of "cirrhosis with ascites" presenting at Department of Gastroenterology, Mahatma Gandhi Medical College, Jaipur (Rajasthan). International Classification of Diseases (ICD)-10 codes were used for diagnosis. Records of SBP was reviewed, based on ascitic fluid examination report in these subjects. Two study groups of cirrhotic subjects with and without SBP were formed. In each of the two study groups, 143 subjects, were enrolled by matching for age, year of admission and Child-Pugh-Turcotte (CPT) class. Diagnosis of SBP (cases) required  $\geq 250$  polymorphonuclear white blood cells (PMNs) per cubic millimeter with or without a positive culture of the ascitic fluid. Subjects in non-SBP group (controls) required paracentesis fluid with PMN count  $< 250$  cells/mm<sup>3</sup> and a negative culture.

We excluded subjects with an age below 18 years, those having unreliable medication record, antibiotic use within last two weeks, immunosuppressant use, GI bleed within last 14 days, history of malignancy other than hepatocellular carcinoma (HCC) within the last 5 years, history of prior SBP, organ transplant and HIV infection.

### Data collection

Socio-demographic data, reason for hospitalization, etiology and complications of cirrhosis was evaluated. The laboratory blood tests including total bilirubin, albumin, international normalized ratio (INR), creatinine and sodium levels on admission. Ascitic fluid data included polymorphonuclear neutrophils, protein levels and culture.

### PPI use and indication definitions

Subjects using any PPI for at least two week prior to admission (documented as per admission notes) were considered PPI users, remaining were PPI non-users. An "appropriate PPI use" was defined as PPI use for established FDA-approved indications like gastro-esophageal reflux disease symptoms, erosive esophagitis, risk reduction NSAID induced gastric ulcer, *H. pylori* eradication, peptic ulcer disease, other causes like history of life-threatening non-variceal bleeding, Barrett's

esophagus and prophylaxis following variceal band ligation.

### Statistical analysis

McNemar's paired test and unpaired t-test were used to evaluate the nominal and continuous data respectively. Mann-Whitney U test was used for nonparametric data. A p value  $< 0.05$  was considered significant. MELD scores were calculated in accordance with method used by the United Network for organ sharing.

## RESULTS

The records of 1051 subjects of cirrhosis with ascites was reviewed, paracentesis-proven SBP was confirmed in 239 subjects. Antibiotics was started in all such cases. 31 subjects were excluded because they had experienced a previous SBP episode, 28 because of prior antibiotic use, 16 because of bleeding in last 2 weeks, 13 because they were on immunosuppressant medication and 8 because of unreliable medication record. The remaining 143 cases were then matched according to CPT class, age and year of admission with 143 cirrhotic patients with ascites without SBP. 113 (79.02%) in both groups were CTP class C, remaining were CTP class B. The reason for admission of subjects without SBP were ascites (30.07%, 43), hepatic encephalopathy (35.66%, 51), renal insufficiency (20.28%, 29), alcoholic hepatitis (11.89%, 17) and pre-transplant evaluation (2.1%, 3).

The clinical characteristics of the SBP and non SBP group was summarized in Table 1. The PMN count in ascitic fluid of subjects with SBP ( $984 \pm 278$ /ml) was significantly higher than those without SBP ( $44 \pm 28$ /ml,  $p < 0.001$ ). A significant lower ascitic fluid protein concentration ( $1.1 \pm 0.4$  gm/dl) was seen in subjects with SBP as compared to those without ( $1.7 \pm 0.8$  gm/dl) ( $p = 0.03$ ), suggesting its protective role.

Proportion of subjects using PPI prior to admission was 69.23% in SBP group, which was significant compared to only 35.66% in cirrhotics with no SBP ( $p = 0.0001$ ). Inappropriate PPI use (Table 2) was found in 58.59% among SBP group (58 of 99 cases) compared with 54.9% of non-SBP group (28 of 51 controls) ( $p = 0.6$ ). Only 49 (34.27%) subjects with SBP had positive ascitic fluid culture reports, 29 (59.18%) of which had gram negative organisms as compared with 20 (40.82%) gram positive organisms. No significant difference was observed in PPI use ( $p = 0.2$ ) between Gram-positive and Gram-negative micro-organisms in SBP. PPI use (Table 3) was an independent risk factor for SBP on multivariate analysis (OR 2.24, 95% CI: 1.01-4.24;  $p = 0.033$ ).

Beta blocker use was protective against development of SBP ( $p < 0.001$ ). On multivariate analysis, beta blocker use (at least 4 weeks) demonstrated a protective role for SBP (OR 0.58; 95% CI: 0.4-0.8;  $p = 0.001$ ).

**Table 1: Clinical and laboratory parameters from subjects with spontaneous bacterial peritonitis (SBP) and controls.**

Variables	SBP (n=143)	NO SBP (n=143)	p Value
Age (years)	52±11	51±12	0.59
Male gender (%)	98 (68.53)	90 (62.94)	0.41
H/O variceal bleed (%)	61 (42.66)	56 (39.16)	0.53
H/O hepatic encephalopathy (%)	47 (32.87)	51 (35.66)	0.77
Child Turcotte Pugh (CTP) score (Median)	11 (8-14)	11 (8-15)	0.92
MELD	15.4±4.2	13.1±3.7	0.6
Alcoholic cirrhosis (%)	66 (46.15)	61 (42.66)	0.84
HBV/HCV Cirrhosis (%)	38 (26.57)	33 (23.08)	0.55
Bilirubin (mg/dl)	3.7±1.1	4.4±1.3	0.53
Creatinine (mg/dl)	1.2±0.4	1.4±0.3	0.53
Ascitic fluid protein (g/dl)	1.1±0.4	1.7±0.8	0.03*
PPI Use (%)	99 (69.23)	51 (35.66)	0.0001*
H2 Blocker Use (%)	9 (6.29)	8 (5.59)	0.6
Beta blocker use (at least 4 weeks) (%)	41 (28.67)	66 (46.15)	<0.001*

\*p<0.05, MELD, model for end-stage liver disease; H 2 blocker, blockers of type 2 histamine receptor; PPI, proton pump inhibitor; SBP, spontaneous bacterial peritonitis

**Table 2: Evaluation of PPI as risk factors for spontaneous bacterial peritonitis.**

	Odds ratio (95% CI)	p value
<b>Univariate analysis</b>		
PPI use	2.2 (1.09-4.3)	0.02*
<b>Multivariate analysis</b>		
PPI Use	2.24 (1.01-4.24)	0.033*
Beta blocker use (at least 4 weeks)	0.58 (0.4-0.8)	0.001*

\* p<0.05

**Table 3: Details of PPI use.**

PPI use	SBP + PPI User (n=99)	Non SBP + PPI user (n=51)	p value
Inappropriate PPI use (%)	58 (58.59)	28 (54.9)	0.6
Appropriate PPI use (%)	41 (41.41)	23 (45.1)	0.84

PPI, proton pump inhibitors; SBP, spontaneous bacterial peritonitis

## DISCUSSION

In our retrospective case control study, PPI use was associated with SBP in subjects with cirrhotic ascites. Also, ascitic fluid protein was demonstrated to have a protective effect against SBP. To our knowledge, this is the first Indian study, which is well designed, with adequately large study sample to evaluate the association of PPI use with development of SBP in subjects having cirrhotic ascites.

In year 2008, Campbell et al first evaluated SBP in a retrospective case-control study of 116 cirrhotic patients and did not find any association between PPI use and SBP (OR 1.22, P=0.64).<sup>14</sup> However, the study had a very small number of patients with SBP (32 of 116) and MELD score was significantly higher in the SBP group (P=0.002) as compared with non-SBP group. In 2009, Bajaj et al in 70 patients with comparable MELD and CTP scores in both SBP and non-SBP group, suggested that PPI use was independently associated with SBP (OR 4.31, p=0.003) and ascitic fluid protein concentration was protective.<sup>15</sup> Similar result has since been shown in several studies.<sup>16-18</sup> Goel et al in Cleveland, Ohio suggested that patients who did not use PPI in the previous 90 days were 71% less likely to develop SBP than those who used PPI in the previous seven days (OR 0.29, p 0.004).<sup>16</sup> Choi et al, while comparing 83 patients having SBP with 93 controls who did not have SBP, suggested CPT class C, high MELD score and PPI use (OR 3.44, P=0.025) were independent risk factors for SBP.<sup>17</sup> A recent meta-analysis including eight studies (n=3815) supported our results, suggesting that cirrhotic patients on PPI had approximately three times the risk of developing SBP compared with patients not receiving PPIs (OR 3.15 (95% CI 2.09 to 4.74)).<sup>19</sup>

This is the only Indian study till date to evaluate this correlation, in a setting where PPIs are freely prescribed, often without proper indications and are available over the counter. The good safety profile of PPIs allows them to be freely used without proper indication and adequate diagnosis. PPIs are often prescribed in decompensated cirrhotics with ascites, complaining of abdominal discomfort and dull ache, which may have been caused by abdominal distention or underlying SBP. Proton pump inhibitors (PPIs) potentially inhibit gastric acid secretion

and lowers the defenses against ingested microorganisms. Several pathophysiological mechanisms have been postulated for predisposition for SBP in cirrhotics with PPI use. Small intestinal bacterial overgrowth has been found to be associated with PPI use in several studies.<sup>20,21</sup> An impaired intestinal permeability, increases the risk of translocation and bacteremia, as has been shown in animal and human studies.<sup>22,23</sup> Evidence suggests that PPIs may suppress the neutrophil activity and innate immunity.<sup>24</sup> Cirrhotics are at a unique risk pertaining to increased intestinal permeability, delayed gastric emptying and fact that PPI metabolism may be significantly impaired (except rabeprazole) leading to higher exposure in this special subgroup.

Reiberger T et al in 2013, suggested that beta-blockers restrict bacterial translocation by decreasing intestinal permeability in humans.<sup>25</sup> Similar to our results, few other studies suggest that use of beta blockers decreases the prevalence of SBP (Senzolo M et al, Lebrech D et al, Lo GH et al, Cholongitas E et al).<sup>26-29</sup> To our knowledge this is the first Indian study, to evaluate the role of beta blocker in SBP in adequately large sample of Indian cirrhotics.

We matched our cases and controls for age, CTP scores, year of admission and eliminated potential confounding factors such as upper GI bleeding or prior antibiotic use. This was important considering that higher CTP scores were associated with greater SBP risk, which may have otherwise acted as a confounding factor. Year of admission was matched to adjust for PPI prescribing habits, also we controlled for upper GI bleed and prior antibiotic use. These results open new horizons for research in prospective multicenter trials which may go a long way in limiting cirrhotic complications and morbidity.

## CONCLUSION

Our study demonstrated that use of PPI in decompensated cirrhotics with ascites is an independent risk factor for developing SBP, whereas beta blockers and ascitic fluid protein protects against development of SBP.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Committee*

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**Cite this article as:** Rajender A, Choudhary P, Mathur S, Bhargava R, Upadhyay S, Nepalia S. Proton pump inhibitor: a risk factor for spontaneous bacterial peritonitis in Indian cirrhotics decompensated with ascites. *Int J Res Med Sci* 2019;7:378-82.