ORIGINAL ARTICLE

Comparative Study of Spontaneous Bacterial Peritonitis in Cirrhosis Patients Managed with and without Proton Pump Inhibitors

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ABSTRACT

Background: Spontaneous bacterial peritonitis (SBP) is one of the most serious complications of cirrhoticpatients. A few studies have shown that use of proton pump inhibitors (PPI) may increase the risk of occurrence of SBP in cirrhotic patients. However, controversial results have been obtained in the last decades.
Aim: To compare the frequency of Spontaneous Bacterial Peritonitis (SBP) with and without Proton Pump Inhibitors (PPI) in patients of cirrhosis with ascetic fluid.
Study Design: Randomized controlled trial
Settings: Department of Medicine, Mayo Hospital Lahore
Duration: June 2016- December 2016
Methods: Two hundred patients fulfilling the selection were enrolled from Department of Medicine, Mayo Hospital Lahore after taking informed consent. Demographic data including name, age, gender and duration of cirrhosis was noted. Then patients were randomly divided in two groups by using lottery method. One group was given proton pump inhibitors along with standard therapy for a period of 3 months while the other group was given only standard therapy and followed over a period of 3 months. After 3 months, patients were again be evaluated and ascetic fluid was obtained through standard procedure. All samples collected were sent to the laboratory for confirmation of bacteria. Reports were assessed and patients were labeled as positive or negative for SBP.
Results: In this study it was observed that patients who were using PPI among them frequency of SBP was 32% while those patients who were not using PPI among them frequency of SBP was 12% only. Use of PPI among patients presenting with liver cirrhosis had significantly higher rate for SBP. The same trend was seen in all age groups that patients on PPI had higher frequency for SBP but statistical significance was seen in patients in age group 31-40 years of age. Male and female patients and duration of disease showed the same trend that PPI users had higher frequency for SBP and statistically significance was not seen for female patients and patients with disease duration 7-10 years.
Conclusion: PPI use was significantly associated with an increased overall risk of spontaneous bacterial peritonitis. So it is of core importance that PPIs should be used judiciously with regard to appropriate indications and duration in cirrhotic patients.
Keywords: Spontaneous Bacterial Peritonitis, Proton Pump Inhibitors, Cirrhosis, Ascitic fluid.

INTRODUCTION

Liver disease is a major catastrophe worldwide and especially in the developing world, where hygiene, socioeconomic status and literacy have always been a hurdle in the effective prevention of the community against infectious diseases. Cirrhosis can be defined as an irreversible process of hepatocellular injury resulting in fibrosis and nodular regeneration of liver[1]. Cirrhosis of liver is becoming more and more prevalent in our country due to the increasing incidence of Hepatitis C[2]. Moreover cirrhosis is a common cause of mortality among Pakistani population and a frequent cause of hospital admissions[3]. Cirrhosis has an incidence of 3.1%[4] and a prevalence of 234,112 people in Pakistan[5].

Cirrhosis can lead to ascites due to portal hypertension and hypoalbuminemia[6]. Overall prevalence of spontaneous bacterial peritonitis (SBP) in cirrhosis is 8.7%; in in-patients it is 11.7% and in out-patients it is 3.1%[7]. SBP can develop in cirrhotic patients with ascetic fluid analysis showing a total white cell count of up to 500 cells/µL with a high proportion of polymorphonuclear cells (≥ 250/µL) and a protein concentration of 1 g/dL (10 g/L) or less[8]. Pathogenesis of SBP in cirrhosis can be explained by decreased levels of opsonins in ascitic fluid[8].

Proton pump inhibitors (PPI) are commonly used drugs in cirrhotic patients, but it has been seen in different clinical studies that use of PPI is associated with high risk of SBP in cirrhotic patients[9].

In a study, it has been noticed that among PPI users, SBP was present in 22.5% cases while among non-PPI users, SBP was present in 21.5% cases. The difference was reported to be insignificant (P=0.176)[10].
Another study showed that among PPI users, SBP was present in 30.2% cases while among non-PPI users, SBP was present in 31.8% cases. The difference was reported to be insignificant (P>0.05)[11,12].

Rationale of this study is to compare the frequency of Spontaneous Bacterial Peritonitis with and without Proton Pump Inhibitors in patients of cirrhosis with ascetic fluid. The implication of my study is if PPI use is found to be associated with increased incidence of SBP in cirrhotic patients with ascites then we should emphasize on opposing excessive use of proton pump inhibitors in cirrhotic patients. But literature has reported contradictory results, as some showed that whether PPI is given or not, there is no difference in frequency of SBP while others

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showing that SBP rate is high with PPI use. As no such study has been carried out in local setting, so that we could be able to negate the use of PPI among cirrhotic patients with ascites. So we want to conduct this study, first to confirm whether SBP is linked to PPI use and second we will also get local data which will help in future whether to prescribe PPI in such critical cases or not.

Operational definitions:

Cirrhosis with ascites: It was defined as Presence of any three or more of the following: jaundice (Bilirubin level>2mg/dl) anorexia, tiredness and weakness, sudden weight loss (>5kg in 1month, on history), and nodules and irregular and increase echogenicity of the liver confirmed on ultrasonography and also presence -of fluid in liver region contaminated with bacterium (on fluid culture) (>10/HPF)

Proton Pump Inhibitor: It was defined as use of pre-hospital acid suppressive therapy like PPI up to 40mg/24hrs for 3 months.

Spontaneous Bacterial Peritonitis: It was labeled as the infection of ascitic fluid with ascitic fluid analysis showing a white cell count of up to 500 cells/µL with a high proportion of polymorphonuclear cells (≥250/µL) and a protein concentration of ≤1 g/dL.

MATERIAL AND METHODS

It was randomized controlled study conducted in the Departments of Medicine, Mayo Hospital Lahore during June 2016 and December 2016. Sample size of 200 cases; 100 cases in each group was calculated with 80% power of study, 15% level of significance and taking expected percentage of SBP i.e. 22.5% in cases on PPI and 6% in cases on standard therapy only. Non-probability consecutive sampling technique was used. Both male and female patient between ages of 15-65 years having cirrhosis with ascites, diagnosed at least 6months ago were included in the study.

Exclusion criteria

1. Upper GI bleed (on endoscopy)
2. Hepatic encephalopathy (on medical record)
3. Hepatorenal syndrome (on medical record)
4. Patients taking antibiotics (on medical record)

Data collection procedure: 200 patients fulfilling the selection were enrolled from department of Medicine, Mayo Hospital Lahore after taking informed consent. Demographic data including name, age, gender and duration of cirrhosis was noted. Then patients were randomly divided in two groups by using lottery method. One group was given proton pump inhibitors along with standard therapy for a period of 3 months while the other group was given only standard therapy and followed over a period of 3 months. After 3 months, patients were again to be evaluated and ascitic fluid was obtained through standard procedure. All samples were sent to the laboratory for confirmation of bacteria. Reports were assessed and patients were labeled as positive or negative for SBP.

Data analysis: All the data was entered and analyzed by using SPSS version 21. Numerical variables as age and duration of cirrhosis was represented as Mean±SD and categorical variables as gender and SBP was expressed as frequency and percentages. To compare the frequency of SBP in both groups, Chi-square test was used. P-value ≤0.05 was considered as statistically significant. Chi-square was applied taking p≤0.05 as significant statistically.

RESULTS

Mean age of patients with and without PPI treatment was 41.12±12.22 and 44.12±12.37 years. Patients on PPI treatment among them 41 were male and 59 were females. While patients not receiving PPI treatment among them 55 were male and 45 were females. Mean duration of disease of patients with and without PPI treatment was 5.90±2.82 and 5.61±2.76. Frequency of spontaneous bacterial peritonitis in patients receiving PPI was 32% and those who did not receive PPI therapy among them frequency of SBP was 12% only. Patients on PPI therapy had significantly higher frequency of SBP. i.e. p-value=0.001(Table 1).

Patients taking PPI in all age groups had higher frequency for SBP but patients in the age group 31-40 years showed statistical significance for SBP who were using PPI. i.e. 20-30: PPI+: 25% vs. PPI-: 18.2% (p-value=0.575), 31-40:53.8% vs. PPI-: 5.9%(p-value=0.001), 41-45:22.2% vs. PPI-: 11.1%(p-value=0.273) & 51-60:35.3% vs. PPI-: 17.4%(p-value=0.196). Among male and female patients frequency of SBP was higher in PPI group but statistical significance was seen in only male patients. i.e., Male: PPI+: 29.3% vs. PPI-: 7.3% (p-value=0.004), Female:33.9% vs. PPI-: 17.8%(p-value=0.066) (Table 2)

Patients who were using PPI and their duration of disease was 1-3 and 4-6 among them frequency of SBP was significantly higher however patients whose duration of disease was 7-10 among them no statistically significant association was seen for SBP in both groups. i.e., 1-3: PPI+: 40% vs. PPI-: 7.4% (p-value=0.005), 4-6: 42.9% vs. PPI-: 16.2% (p-value=0.017), 7-10: 21.3% vs. PPI-: 11.1%(p-value=0.220) (Table-3)

Table1: SBP with and without PPI in patients of cirrhosis with ascetic fluid

SBP	PPI+	PPI-	Total
Yes	32(32%)	12(12%)	44
No	68(68%)	88(88%)	156
Total	100	100	200

Chi-Square Test=11.65 p-value=0.001

Table-2: SBP with and without PPIin patients of cirrhosis with ascetic fluid stratified for gender

SBP	PPI+	PPI-	P value
Male			
Present	12(29.3%)	4(7.3%)	0.004
Absent	29(70.7%)	51(92.7%)	
Female			
Present	20(33.9%)	8(17.8%)	0.066
Absent	39(66.1%)	37(82.2%)	

Table 3: SBP with and without PPIin patients of cirrhosis with ascetic fluid stratified for duration of disease

SBP	PPI+	PPI-	P value
Duration 1-3			
Present	10(40%)	2(7.4%)	0.005
Absent	15(60%)	25(92.6%)	
Duration 4-6			
Present	12(42.9%)	6(16.2%)	0.017
Absent	16(57.1%)	31(83.8%)	
Duration 7-10			
Present	10(21.3%)	4(11.1%)	0.220
Absent	37(78.7%)	32(88.9%)	

DISCUSSION

PPI is the most widely used antacids and its plays inhibition of gastric acid secretion by blocking parietal cells H+/K+-ATP enzyme. It is widely used in peptic ulcer, gastroesophageal reflux or non-ulcer dyspepsia patients.[13] However, more and more evidences about PPI have implied a relationship between the application of PPI and the potential risk of adverse reactions such as hip fracture, damaged about the peristalsis of the stomach, interference the function of neutrophils, intestinal infections, community-acquired pneumonia and SBP[14].

Gastric acid can purify stomach and proximal small intestine, and play an important role in resisting the intestinal pathogens. However, the changes of gastric pH induced by antacids may damage the gastric protective barrier; alter the normal flora of the gastrointestinal pathogens and aggregate pathogenic bacteria, which increases the risk of infection such as pneumonia and diarrhea caused by Clostridium diffcile and salmonella[15].

In this study it was observed that patients who were using PPI among them frequency of SBP was 32% while those patients who were not using PPI among them frequency of SBP was 12% only. Use of PPI among patients presenting with liver cirrhosis had significantly higher rate for SBP. The same trend was seen in all age groups that patients on PPI had higher frequency for SBP but statistical significane was seen in patients in age group 31-40 years of age. Male and female patients and duration of disease showed the same trend that PPI users had higher frequency for SBP and statistically significance was not seen for female patients and patients with disease duration 7-10.

A few studies have shown the risk of the SBP occurrence after PPI therapy in cirrhotic patients and the relationship has been assessed in a small sample[16]. However, controversial results have been obtained in the last decades. While Goel et al. reported that PPIs were found to increase the incidence of SBP in cirrhotic patients signifcantly[17].

Terg R et al. and Campbell et al. reported that the use of PPI did not affect the incidence of SBP.[18] A few studies assessed the relationship between the risk development of SBP and PPI therapy by meta-analysis, but these studies did not touch on different ethnic groups, nor included the results of the recent two years[19]. Results of this study are consistent with the findings of Goel et al but totally contradicting the findings of Terg R et al. and Campbell et al findings[20].

Bajaj JS in his study reported that among PPI users, SBP was present in 22.5% cases while among non-PPI users, SBP was present in 21.5% cases. The difference was reported to be insignificant (P=0.176).[10] But in this study patients using PPI among them SBP was significantly higher as that of patients who were not using PPI i.e., PPI+: 32% vs. PPI-:12%, p-value=0.001. Although these results confirms the findings of Bajaj JS in terms of higher rate of SBP among PPI users but in terms of statistical significance it contradicts.

daSilva Miozzo SA study showed that among PPI users, SBP was present in 30.2% cases while among non-PPI users, SBP was present in 31.8% cases. The difference was reported to be insignificant (P>0.05)[11] Results of this study contradicts the findings of daSilva Miozzo SA as he has shown higher rate of SBP among non-PPI users which is totally opposing to findings of this study.

But study by Aditi A showed that the SBP incidence rate was significantly higher in the PPI group than in the non-PPI group (10.8% vs. 6%, P=0.038)[12.] These findings completely support the results of this study as it showed higher incidence of SPB among PPI users with statistical significance[21].

Previously 2 meta-analyses that is relevant to this topic. The earliest meta-analysis, published in 2011, only included 4 studies that examined 772 patients. The more recent meta-analysis only included 8 studies.

Both studies failed to explore sources of heterogeneity and did not evaluate data concerning dose or duration. The difference may be due to the patients with significant liver damage in the former two studies. In addition, the mutant strains and its types, dosage of drugs may affect the results during treatment. So far, the mechanism associated with the incidence of SBP and PPI has remained unclear. There was a hypothesis that overgrowth of gastrointestinal flora after colonization during acid inhibitor therapy may be the cause of increasing SBP by acid inhibitor drugs. Regardless of the key mechanisms of SBP induced by PPI, the use of PPI may increase the incidence of SBP in cirrhotic patients.

In conclusion, PPI can be used in the treatment of peptic ulcer, gastroesophageal reflux, and other indications. However, PPI therapy should be administered with a caution in cirrhotic patients. Future studies maybe need to clarify the relationship between the occurrence of SBP and the type and dose of PPI in cirrhotic patients.

CONCLUSION

Study demonstrated that PPI use was significantly associated with an increased overall risk of spontaneous bacterial peritonitis. So, it is of core importance that PPIs should be used judiciously with regard to appropriate indications and duration in cirrhotic patients.

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