A Study on Chronic Proton Pump Inhibitor Usage and Small Intestinal Bacterial Overgrowth (SIBO)

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ABSTRACT

Introduction: Small Intestinal Bacterial Overgrowth (SIBO) has a wide clinical spectrum, and may be associated with both maldigestion and malabsorption. Proton Pump Inhibitors (PPI) are one of the most widely prescribed medications in view of their safety profile. This has lead to their indiscriminate usage, giving rise to growing concerns of SIBO in the setting of long term PPI usage.

Aim: To evaluate the correlation between chronic PPI usage (>2 months) and SIBO, as diagnosed by duodenal aspirate cultures.

Materials and Methods: A total of 80 subjects were included in this prospective observational study. All patients were subjected to Upper Gastrointestinal Endoscopy (UGIE) and one mL duodenal aspirate was collected for bacterial cultures. A growth of more than 10^5 CFU/mL was considered positive for SIBO. The inter-group statistical comparison was done using Chi-square test, and a p-value of <0.05 was taken as significant.

Results: The mean age of the entire study group was 45.4 years. Gender wise, 72.5% of the patients were males. Gastritis, as detected by endoscopy was seen in 37.5% patients, and 35% patients had infection with *H.pylori.* The use of NSAIDS was noted amongst 36% of the study population. The most common PPI used was Pantoprazole and majority of the patients had used it for greater than six months. Flatulence was the predominant symptom of SIBO in 41% study subjects. On UGIE, 34 out of 80 (42.5%) patients had abnormal findings and 19 out of 80 (23.8%) patients had SIBO as per positive duodenal aspirate culture reports (>10^5 CFU per mL). Based on various intergroup analysis, SIBO was not significantly (p>0.05), associated with any form of PPI usage, *H.pylori* infection, NSAID use or smoking/alcohol abuse.

Conclusion: It was observed in this single center study that, SIBO was not associated with duration/ dose/ type of PPI usage. This study needs further validation with a case-control design in a diverse patient population.

Keywords: Duodenal aspirate, Endoscopy, Malabsorption

INTRODUCTION

SIBO is a heterogeneous syndrome characterised by an increased number and/or abnormal type of bacteria in the small bowel. SIBO represents the overgrowth of bacterial species in the proximal small gut. As a result of SIBO, fermentation of dietary carbohydrates by these bacteria leads to over production of gas and to the generation of symptoms of maldigestion or malabsorption.

Proton Pump Inhibitors (PPI) are one of the most widely prescribed medications in view of their safety profile and because of the huge number of patients who present to Medical/Gastroenterology OPD with dyspeptic symptoms [1]. PPIs produce profound suppression of gastric acid secretion, and loss of the natural acid barrier, which raises a number of problems including the overgrowth of bacteria in the stomach and duodenal fluids. Some of the other common side effects associated with PPI are, interstitial nephritis, hepatitis [2] fundal polyps [3], risk of osteopenia [4] and iron/vitamin malabsorption [5,6].

However, of late there is a growing concern of association of long term PPI use with SIBO. Normally, SIBO is prevented by the action of the intestinal immune system, gastric acid and pancreatic enzyme secretion, along with normal intestinal motility, and ileo-cecal valve function. There have been a lot of truncated studies [7,8] conducted in India showing association between SIBO and Irritable Bowel Syndrome (IBS) like symptoms, but a definitive study linking SIBO with PPI use is lacking in India. Data from western studies have shown mixed results [9-11].

Hence, this study was designed, to try and look at the correlation between chronic PPI usage and SIBO, as diagnosed by duodenal aspirate cultures.

MATERIALS AND METHODS

The study was a prospective observational design, carried out at a Tertiary care Gastroenterology center of the Armed forces. The study period was for two years (July 16 to July 18). The study population included consecutive adult patients undergoing UGIE at the Gastroenterology center, and who were on PPI therapy for at least two months or more. Using data from a previous study [9] and assuming a prevalence of SIBO in PPI users at 50%, along with a 10% margin of error and a 95% confidence interval, a sample size of 80 was arrived at.

The gold standard for SIBO diagnosis is considered aspiration and culture of duodenal content. The diagnosis of SIBO gets established when the bacterial count in proximal duodenal aspirate culture becomes $\geq 10^5$ bacterial CFU (colony forming units) per mL [5]. At endoscopy, duodenal aspirate was obtained via an aspiration catheter and at least 1 mL small bowel fluid was suctioned into a sterile container. The aspirate was sent to lab and cultured for aerobic bacteria. Growth of >10^5 cfu/mL was considered positive. All the test reports were informed back to the patients and those with positive cultures were called to OPD for review of medications and a course of antibiotics as per the treating clinicians' discretion.

The study was approved by the Institutional Ethics Committee (CHAFB/26/2016), and a written informed consent was obtained from all the study participants.

The inclusion criteria were:

a)   Age >18 years;

b)   Patients on PPI for more than two months; and

c)   Patients willing to undergo UGIE and Duodenal aspiration.

The exclusion criteria were:

a) Patients who were HIV/HBsAg/HCV positive;

b) Patients who were treated with antibiotics or steroids in the previous three months;

c) Patients with contraindication for UGIE;

d) Inflammatory bowel disease;

e) Celiac disease;

f) Chronic Liver disease;

g) Pregnancy;

h) Intra abdominal malignancy;

i) Diabetes mellitus.

STATISTICAL ANALYSIS

The data was entered in MS Excel before statistical analysis using Statistical Package for Social Sciences (SPSS ver 21.0). Duodenal aspirate culture results were correlated with the use of PPIs. The data on categorical variables were shown as n (% of cases) and the data on continuous variables were presented as Mean and Standard deviation (SD). The inter-group statistical comparison of categorical variables was done using Chi-square test and, p-values less than 0.05 were considered to be statistically significant.

RESULTS

A total of 80 cases were included in the study. The Mean±SD of age of the entire study group was 45.4±14.2 years. The male to female ratio was 2.6:1. Of the 80 cases who underwent UGIE, the most common finding was gastritis; seen in 30 cases (37.5%). *H. pylori* infection was detected in 28 (35%) cases. The most common PPI used was Pantoprazole, in 44 (55%) cases. Most patients were on PPI for 6-12 months. Details of the baseline data are given in [Table/Fig-1].

Of the 80 cases studied, 19 cases (23.8%) had positive duodenal aspirate culture examination and 61 cases (76.3%) had a negative duodenal aspirate culture examination. The distribution of prevalence of SIBO, as assessed by Duodenal aspirate culture did not differ significantly across various durations of PPI usage [Table/Fig-2]. The prevalence of SIBO also did not differ significantly between group of cases who had treatment for *H.pylori* infection and those who did not have it [Table/Fig-3]. The distribution of SIBO did not differ significantly according to history of use of NSAIDs [Table/Fig-4]. SIBO also did not differ significantly according to type of personal habits like smoking or alcohol usage [Table/Fig-5].

Characteristics	Numbers
Mean±SD	45.4±14.2 yrs
Range of age	19-72 yrs
Male n (%)	58 (72.5%)
Female n (%)	22 (27.5%)
Indication of UGIE n (%)	
Dyspepsia	43 (53.7%)
Gastro oesophageal reflux disease	34 (42.5%)
GI bleed	9 (11.2%)
UGIE finding n (%)	
Gastric ulcer	8 (10%)
Duodenal ulcer	4 (5%)
Gastritis	30 (37.5%)
Normal study	38 (47.5%)
H. pylori Infection n (%)	
Present	28 (35%)
Absent	52 (65%)

Type of PPI Usage n (%)	
Pantoprazole	44 (55.0%)
Omeprazole	26 (32.5%)
Rabeprazole	10 (2.5%)
Duration of PPI usage	
>6 months	19 (23.8%)
6-12 months	24 (30.0%)
12–18 months	18 (22.5%)
18–24 months	05 (6.3%)
>24 months	14 (17.5%)
Smoking and alcohol usage n (%)	
Non smoker and non drinker	34 (42.5%)
Smoker only	7 (8.8%)
Drinker only	17 (21.3%)
Smoker and drinker	22 (27.5%)

[Table/Fig-1]: Baseline characteristics of patients.

Duodenal aspirate culture				
	Negative	Positive	Total	p-value
Duration (Months)	N (%)	N (%)	N (%)	
2-6 Months	15 (79)	4 (21)	19 (100)	
6-12 Months	18 (75)	6 (25)	24 (100)	
12-18 Months	14 (78)	4 (22)	18 (100)	0.595
18-24 Months	5 (100)	0 (0)	5 (100)	
>24 Months	9 (64)	5 (36)	14 (100)	
Total	61 (76.3)	19 (24)	80 (100)	

[Table/Fig-2]: Distribution and prevalence of SIBO according to duration of PPI usage.

Duodenal aspirate culture				
	Negative	Positive	Total	p-value
Past exposure to anti *H. pylori* treatment	N (%)	N (%)	N (%)	
No	42 (81)	10 (19)	52 (100)	
Yes	19 (68)	9 (32)	28 (100)	0.196
Total	61 (76)	19 (24)	80 (100)	

[Table/Fig-3]: Distribution and prevalence of SIBO according to the past history of exposure to anti *H.pylori* treatment.

Duodenal aspirate culture				
	Negative	Positive	Total	p-value
Use of NSAIDs	N (%)	N (%)	N (%)	
No	32 (73)	12 (27)	44 (100)	
Yes	29 (81)	7 (19)	36 (100)	0.413
Total	61 (76)	19 (24)	80 (100)	

[Table/Fig-4]: Distribution and prevalence of SIBO according to the history of use of NSAID.

Duodenal aspirate culture				
	Negative	Positive	Total	p-value
Habit	N (%)	N (%)	N	
Nil	27 (79)	7 (21)	34 (100)	
Smoking	7 (100)	0 (0)	7 (100)	
Alcohol	13 (77)	4 (23)	17 (100)	0.231
Smoking+Alcohol	14 (64)	8 (36)	22 (100)	
Total	61 (76)	19 (24)	80 (100)	

[Table/Fig-5]: Distribution and prevalence of SIBO according to personal habits.

DISCUSSION

The aim of this study was to try and establish a relationship of SIBO with long term PPI therapy. This prospective observational study recruited (n=80) consecutive subjects who were on chronic

Author	Country	Subjects		Duration of PPI use	Test used	SIBO		p-value
		On PPI (n)	Control (n)			On PPI n (%)	Control n (%)	
Choung RS et al., [16]	USA	249	426	Any duration	Aspirate culture	25 (10%)	29 (6.8%)	p>0.05
Jacobs C et al., [15]	USA	65	85	Any duration	Aspirate culture	21 (32%)	16 (19%)	p<0.05
Franco DL et al., [10]	USA	466	797	Mean of 23 months	Aspirate culture	202 (43%)	264 (33%)	p>0.05
Giamarellos B et al., [11]	Greece	184	713	>1 month	Aspirate culture	35 (19%)	123 (17%)	p>0.05
Revaiah PC et al., [7]	India	91	-	Mean of six months	Glucose hydrogen breath test (GHBT)	12 (13.18%)	-	p>0.05
Present study	India	80	-	> 2 month	Aspirate culture	19 (24%)	-	p>0.05

[Table/Fig-6]: Comparing data with recent studies on SIBO and PPI usage [7,10,11,15,16].

PPI therapy (>2 months), and looked at positive duodenal aspirate cultures to establish SIBO, which was diagnosed in 23.7% (19/80) in this study population. SIBO was not associated with duration/dose/type of proton pump inhibitor used.

In a similar study by Lombardo L et al., which involved 200 patients on chronic PPI therapy (>2 months), the prevalence of SIBO was reported much higher at 50% [9]. This significantly higher prevalence could have been due to the method used to diagnose SIBO being the much more sensitive Glucose hydrogen breath test (GHBT), rather than more specific duodenal aspirate culture used in this study. Despite the higher prevalence of SIBO, PPI usage did not significantly correlate with duration or type of PPI used. The symptoms of SIBO were primarily bloating in about 50% of cases, diarrhea in 30%, followed by constipation and abdominal pain in 10%. This was similar to the pattern of symptoms noted in the index study.

In another large retrospective study published from Mayo clinic by Franco DL et al., the authors looked at duodenal aspirate cultures obtained from patients undergoing outpatient UGIE [10]. Duodenal aspirates were obtained in 1,263 patients, and the overall yield for positive (>100,000 cfu/mL) duodenal aspirates was 30%. PPIs were used in 37% (466/1263) of these patients. When looking at only PPI usage in the entire study cohort, its use was significantly higher (52.6%) in patients with culture positive duodenal aspirates than those with culture negative aspirates (30.2%; p<0.0001). However, there was no correlation between diagnosis of SIBO and duration of PPI therapy or the type of PPI used.

In a large prospective study from Athens by Giamarellos B et al., quantitative cultures of duodenal aspirates were performed for aerobic species in 897 consecutive patients undergoing UGIE [11]. The overall frequency of SIBO by culture was 10.6%, when the $\geq 10^5$ cfu/mL diagnostic cut-off was used. Only 184 (20.5%) of these patients had a history of chronic PPI intake. There was no difference between the two groups of patients with and without SIBO, regarding history of PPI intake. There was no association of SIBO with PPI exposure in this large study, similar to the findings in our study. Further, patients with SIBO were older, and had a greater frequency of IBS and Diabetes mellitus.

Using breath samples for hydrogen and methane after glucose challenge (GHBT) Ratuapli SK et al., studied a total of 1191 patients, of which 48% were on PPI. Breath test positivity did not differ significantly between PPI users and non-users [12]. In another study by Erdagon A et al., diagnostic yield of SIBO by duodenal aspirate culture was 45% vis-à-vis 27% by Breath test (GHBT) and both tests did not show significant association of SIBO with PPI usage [13]. Looking at the meta-analysis of data from previous studies [14], and comparing with our data from the present study, it is evident that PPI use is not associated with SIBO, irrespective of the diagnostic modality used and duration of PPI therapy.

We tabulated the data from various studies with similar study parameters [Table/Fig-6] [7,10,11,15,16], and found our data to compare favorably with most of the data on the subject, published over the last decade. Except for one study by Jacobs C et al., all other studies have noted no statistically significant association between chronic PPI usage and SIBO [15].

STRENGTH AND LIMITATION

The major strength of our study is the diagnostic modality used for SIBO is duodenal aspirate culture analysis, which is considered to be the gold standard for diagnosing SIBO. The major weakness of our study is the lack of a control arm. Thus, patients on chronic PPI therapy and pre-existing SIBO could not be conclusively excluded from the study population. Also, the lack of anaerobic cultures may have falsely lowered the true prevalence of SIBO in the study population.

CONCLUSION

Based on data from this study, it was concluded that SIBO was not associated with dose, duration or type of PPI used. SIBO was also not associated with previous *H. pylori* infection, NSAID exposure in the past and smoking or alcohol usage. Since this was a hospital based single center observational study without a control arm, further studies with a case-control design will be useful in validating these results in the general population.

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