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TO ESTIMATE THE INCIDENCE OF SMALL INTESTINAL BACTERIAL OVERGROWTH IN PATIENTS WITH LONG TERM PROTON PUMP INHIBITOR USE IN TERTIARY CARE HOSPITAL IN SOUTH INDIA USING HYDROGEN BREATH TEST

Gastroenterology

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ABSTRACT

AIM: To estimate the incidence of small intestinal bacterial overgrowth in patients with long term proton pump inhibitor use in tertiary care hospital in south India using Hydrogen Breath test. **Materials And Methods:** A prospective observational study with 302 patients with a history of PPI intake for long term was conducted for 1 year. The relation between clinical history and complaints, laboratory reports and endoscopy with the incidence of SIBO were evaluated. **Results:** 34 of 304 patients on long term PPI were positive for SIBO (11.25%). Patients with complaints of heartburn, dysphagia and diarrhoea as well as patients with Diabetes mellitus and impaired sugars had a statistically significantly higher risk for SIBO. **Conclusion:** There is a significant risk of SIBO on long term use of PPI. Patients with Diabetes and higher blood sugar levels are especially susceptible to SIBO. Patients should be educated and sensitized to the side effects of PPI and encouraged to use them judiciously.

KEYWORDS

Proton Pump Inhibitor, Small intestinal Bacterial Overgrowth, Glucose Hydrogen Breath Test.

INTRODUCTION

Proton pump inhibitors (PPIs) are commonly used drugs, also, must be stressed that the introduction of generic PPIs into the market has contributed to increase remarkably PPI prescriptions. In addition, as PPIs are now available as OTC in many countries, patients can have free access to them and tend to take these drugs for long periods of time without seeking any medical consultation. Long term PPI use for studies is taken as >8 weeks for treatment failures/clinical context, >6 months for pharmacy-epidemiological studies and >3 years for long term side effects like gastrin levels/gastric HPE[1]. The two major issues are represented by the excessive costs of therapy for both patients and healthcare and the potential risk for their side effects on long-term use which can contribute to gastrointestinal infections, pneumonia, nutrient deficiencies, fractures, spontaneous bacterial peritonitis, and small intestinal bacterial overgrowth (SIBO)[2].

Small intestinal bacterial overgrowth (SIBO) is defined as an abnormally high bacterial population (10^5 - 10^6 colony forming units (CFU)/mL) in the proximal small intestine[3]. Hydrogen breath test is non invasive, simple and safe for detecting high concentrations of bacteria in the small bowel (SIBO)[4].

Many studies presenting a relationship between SIBO and PPI therapy have been done but this association is controversial due to conflicting results from studies conducted to date[5]. With a wide availablity and use of PPI in todays world, our study aimed at incurring the relationship between the use of long term PPI and SIBO using Glucose Hydrogen Breath Test (GHBT).

MATERIALS AND METHODS:

A prospective observational study was conducted from August 2023 to July 2024. After Institutional ethical committee approval and informed written consent, 302 patients with history of PPI intake for long term were selected for the study. A detailed history was taken and clinical examination was done. Patients were evaluated by Hydrogen breath test, and a positive Hydrogen breath test for SIBO was taken as a rise in Hydrogen by >12 ppm from baseline. Patients were evaluated with Blood tests (Complete blood count, Renal and liver function test, Sugar), and as per need urine routine analysis, stool routine analysis, ultrasound abdomen, upper and lower GI endoscopy. The test result and relevant data were collected for analysis.

Inclusion And Exclusion Criteria:

Patients attending the Medical Gastroenterology outpatient department (OPD) aged above 18 years, who had a history of long term PPI (more than 8 weeks) were enrolled in the study. Patients who were pregnant, lactating mothers, recent antibiotic use, respiratory diseases and patients not willing/not able to undergo breath testing were excluded from Hydrogen Breath Testing.

Technique - Glucose Hydrogen Breath Test:

The Gastro+ Gastrolyzer (Bed font–UK) was the instrument used in measuring the hydrogen levels in expired breath. Precautions taken to overcome false negative and false positive results Basal hydrogen breath test was performed after the overnight fast. The subjects were advised to avoid the slowly absorbed carbohydrate diets such as bread, potato, corn or high fiber diet at least for 24 hours prior to GHBT, as the diet could cause delayed excretion of hydrogen in the breath resulting in a false negative result.

Cigarette smoking and physical exercise were also restricted for about 2 hours before and during the test as that could lead to hyperventilation and thereby change in breath hydrogen content. The subjects were also instructed to brush their teeth and rinse their mouth with an antiseptic solution. This was done to eliminate an early hydrogen peak due to the action of oral cavity bacteria on test glucose. Basal breath hydrogen level was measured by averaging the three basal values done on the first visit.

In GHBT, patients were then advised ingestion of 75 grams of glucose dissolved in 200 mL of water. Thereafter, breath hydrogen levels were measured once every 15 minutes for about 2 hours at 15, 30, 45, 60, 75, 90, 105, and 120 minutes. An increase in hydrogen excretion, in parts per million (ppm), following glucose administration, was calculated by subtracting the fasting value from the highest value of hydrogen excretion obtained. A rise of breath hydrogen by more than 12 ppm above basal value following glucose administration was considered positive for SIBO. [6,7]

Statistical Analysis:

Data was collected in MS Excel sheet and statistical analysis was performed using SPSS 16 version of the software. The categorical data was compared using the Fisher exact test and numerical data using Unpaired t test.The SPSS 16 version of the software was used to calculate the data.

RESULTS:

A total of 302 patients with a history of long term PPI use were included in the study. Out of them, 34 were positive for HBT for SIBO. **The incidence of SIBO in patients on long term PPI in the present study is 11.25%.**

Table 1: Clinical Features In Patients Of SIBO

Clinical feature	SIBO (n=34) (%)
Post Prandial Distress	4 (11.7%)
Loss of Weight	7 (20.5%)
Abdominal Pain	15 (44.1%)
Bloating	11 (32.3%)
Heart burn	31 (91.1%)
Dysphagia	3 (8.8%)
Diarrhoea	14 (41.1%)

The mean age of patients with SIBO was 43.2±11.4 years. The patients were predominantly male (n=22; 65%). The most common clinical complaint was heartburn (91%), followed by abdominal pain (44%), diarrhoea (41%), bloating, loss of weight, Post prandial discomfort and dysphagia. (**Table 1**) The laboratory parameters obtained hemoglobin, total count, platelet count, fasting blood sugar, blood urea, serum creatinine, total bilirubin, SGOT, SGPT, total protein and albumin were noted.

Table 2: Demographic Data Of Long Term PPI Users:

SEX	SIBO (n=34)	No SIBO (n=268)	Total	P value
Male	22 (65%)	122 (45%)	144	0.044
Female	12 (35%)	146 (54%)	158	
Total	34	268	302	
Age	**SIBO (34) No SIBO (268)**	**No SIBO**	**P value**	
Years	43.2±11.4	40.56±12.13	0.229 (1.204)	

The test showed negative for SIBO in 268 long term PPI users and the two groups were compared. Demographic findings and laboratory parameters between the two groups are shown in **Table 2**. There was no statistical difference in the age of the two groups. Even though the use of long term PPI was more prevalent in women, SIBO was found to be statistically significant in men.

Table 3: Symptoms In Patients With And Without SIBO

Clinical feature	SIBO	No SIBO	P value
PDS	4 (11.7%)	33(12.3%)	1.00
LOW	7 (20.5%)	65(24.2%)	0.831
Abdominal Pain	15 (44.1%)	74(27.6%)	0.070
Bloating	11 (32.3%)	35(13.1%)	0.008
Heart burn	31 (91.1%)	203(75.7%)	0.048
Dysphagia	3 (8.8%)	3(1.1%)	0.021
Diarrhoea	14 (41.1%)	48(17.9%)	0.003

As shown in **Table – 3**, the most common symptoms in patients on long term PPI was heartburn (77.4%). The other complaints included abdominal pain, loss of appetite, diarrhoea, bloating, Postprandial discomfort and dysphagia. On analysis, the presence of bloating, heartburn, dysphagia and diarrhoea showed a significant increase in the possibility of SIBO. Among the laboratory reports statistically significant difference in the blood glucose levels among the two groups was found. **(Table- 4)**. Similarly, no significant difference in the endoscopic findings was noted. **(Table 5)**

The presence of other risk factors for SIBO like steroid use, comorbidity like diabetes mellitus, thyroid disease, Inflammatory bowel disease and chronic pancreatitis were evaluated and it was noted that the presence of diabetes mellitus had a significant risk for SIBO. No patient with thyroid disease or IBD had SIBO positive in our study.**(Table 6)**

Table 4:: Labratory Finding Of Patients With And Without SIBO

OGD finding	SIBO (n=34)	No SIBO (n=268)	P value
Normal	21	206	0.420
Gastritis	10	45	0.095
Portal Hypertension Gastropathy	3	14	0.061
Hiatus Hernia	0	3	1.0

Table 5:Endoscopic Finding Of Patients.

Risk Factors	SIBO (n=34)	No SIBO (n=268)	Total (n=302)	P value
Diabetes Mellitus	13	48	61	0.010
Steroid intake	13	77	90	0.319
CLD	3	18	21	0.716
Chronic Pancreatitis	1	3	4	0.389

Table 6: Risk Factors And Comorbidities In Patients.

Test	SIBO (34)	No SIBO (268)	P value
Haemoglobin (gm/dl)	10.91±2.82	10.90±2.80	0.991
Total Leucocyte Count	7.60±2.57	7.54±2.60	0.755
Platelet count	316.38±130.61	322.88±122.26	0.772
Bilirubin (mg/dl)	1.01±1.16	0.956±0.774	0.729
SGOT (IU/ml)	28.56±9.17	29.35±9.55	0.660
SGPT (IU/ml)	27.25±6.44	28.77±9.04	0.705
Protein (gm/dl)	5.78±1.28	5.98±1.17	0.359
Albumin (gm/dl)	3.72±0.76	3.84±0.68	0.318
Creatinine (mg/dl)	0.98±0.26	0.96±0.27	0.616
Urea (mg/dl)	28.47±6.81	28.01±7.35	0.731
Sugar (mg/dl)	116±30.8	103±15.20	0.001

DISCUSSION:

Long term proton pump inhibitors (PPI's) defines as use for more than 8 weeks,[1] is common as it is available widely and as an over the counter drug. Its chronic use can alter the resident gut bacteria that help in defense against pathogens, energy production, immune regulation, and nutrient metabolism. This has the potential to alter the normal bacterial milieu at the distal esophagus, stomach, small bowel, and colon; with consequences that may be an alteration in risk for diseases including SIBO. [8,9]

SIBO is defined as a bacterial population in the small intestine exceeding 10^5 –10^6 organisms/mL. Though the culture of jejunal aspirate is deemed the gold standard test to diagnose SIBO, it has few disadvantages being invasive, time-consuming and expensive necessitating sterile technique. The European consensus-based clinical practice guideline recommends Breath testing for the diagnosis of SIBO and does not necessitate stopping PPI before testing.[6.] Hydrogen breath tests use various sugars like glucose and lactulose. Glucose hydrogen breath test was performed in our study. The sensitivity and specificity of the glucose breath test in studies are about 20-93% and 45-86% respectively.

A meta-analysis of many studies revealed that PPI therapy is a significant risk factor for SIBO and a few showed no corelation between PPI use and SIBO[-]. [10,11]

The presence of SIBO was detected in 11.2% of patients with a history of long term PPI. The main symptoms seen in patients with SIBO that had statistical significance include heartburn, diarrhoea, bloating and dysphagia.

Bloating was seen in 34 cases (32% vs 13%) of SIBO positive patients, the plausible mechanisms include increased luminal contents or gas in the intestine, imbalance of gut microbiota leading to food intolerance and decreased abdominal capacity induced by abnormal viscero-somatic responses or anatomical changes. The functional abdominal bloating and distention (FABD) studies have shown symptoms of bloating to reduce with the administration of probiotics and rifiaximin. The specific gut microorganisms associated with FABD have not yet been reported.[12]

The presence of SIBO may be a contributory factor to refractory reflux symptoms owing to endogenous bacterial fermentation leading to methane and hydrogen production in the small bowel. This gas leads to increased belching, regurgitation, heartburn and reflux symptoms. Our study shows Heartburn to be a major symptom in all patients for long term PPI intake and almost all(95%) of patients with SIBO had heartburn. SIBO is a significant cause of refractory GERD or failure of medical treatment, and it may benefit to screen for SIBO, in addition to pH monitoring, before antireflux surgical intervention.[13]

The common symptoms, reported by other studies are abdominal distension, excessive gas accumulation and flatulence, the feeling of

abdominal fullness, diffuse abdominal cramps, and altered bowel habits (predominantly diarrhea).[14] Our study also found that the complaints of diarrhoea were associated with SIBO (41% vs 17%).

The mucosal injury due to bacteria and/or their toxin and metabolites leads to decreased brush border enzyme activity, reduced absorption and inflammation. Deconjugation of bile leads to fat maldigestion and this can lead to diarrhoea and steathorrea. There is associated nutritional deficiency and loss of weight, but in our study, only 20% of patients had loss of weight and was not significant compared to patients without SIBO.

Dysmotility has long been documented as a potential risk factor for bacterial overgrowth. A recent study (n = 150) designed to investigate the role of dysmotility and PPI use in patients with persistent gastrointestinal complaints demonstrated that patients with small intestinal dysmotility have an increased risk for SIBO.[15] SIBO does not cause dysphagia, but oesophagitis and GERD can cause dysphagia. Also, diseases affecting GI motility like systemic sclerosis have an increased risk of SIBO,[16] this may be the reason for the positive association of dysphagia with SIBO in our study.

In our study, the use of PPI in patients with Diabetes Mellitus has a statistically significant risk (P = 0.010) for SIBO.

Similarly, a meta-analysis of 14 studies showed that SIBO is detected in patients with diabetes mellitus more frequently than in controls[17] Also studies noticed patients with SIBO had higher levels of fasting blood glucose and glycated hemoglobin.[18] In our study the mean sugar level of SIBO positive vs negative cases was 116±30.8 mg/dl and 103±15.20 mg/dl respectively. There was a significantly higher risk of SIBO with higher sugar levels (p-value = 0.001).

Patients with Liver disease, Steroid intake and Thyroid disease did not have increased risk of SIBO, the regular follow up with medical practitioners and short term use of antibiotics may be the reason for this. No patients with thyroid disease had SIBO, which may be due to the need for taking tests and visits to healthcare centers, for regular medications.

Limitation:

In our study methane measurement was not performed because we used Bedfont instrument in which only hydrogen measurement could be done. Another limitation of this study was long term follow up was not done. Hence treatment outcome and recurrence of SIBO were not known.

CONCLUSION:

SIBO is common in patients of long term PPI and should be evaluated. GHBT is a non-invasive technique with low cost, and it can be added as an additive test to be included in the evaluation of patients with abdominal complaints. So it helps in ruling out the diagnosis of SIBO and thereby improving the quality of life.

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