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THE EFFECTS OF LONG TERM USE OF PROTON-PUMP INHIBITORS ON THE ENDOSCOPIC AND HISTOLOGICAL FINDINGS OF GASTRIC MUCOSA

Najeeb Abdullrahman*[1], Ismael Hammad[2] and Rana Issa[3]

[1]Department of Gastroenterology, Tishreen University, Faculty of Medicine, Lattakia, Syria.
[2]Department of Gastroenterology, Professor, Tishreen University, Faculty of Medicine, Lattakia, Syria.
[3]Department of Histopathology, Professor, Tishreen University, Faculty of Medicine, Lattakia, Syria.

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***Corresponding author: Najeeb abdullrahman**

Department of Gastroenterology, Tishreen University, Faculty of Medicine, Lattakia, Syria.

ABSTRACT

Background: Proton pump inhibitors (PPIs) are commonly used for the treatment of acid-related disorders. Despite their safe and ease of availability, PPIs can have severe side effects. **Objective:** the present study aims to determine the endoscopic and histopathologic gastric changes in long term users of PPIs. **Materials and Methods:** This is analytical study (Case-Control) conducted in the department of Gastroenterology in Tishreen University Hospital-Lattakia -Syria from September 2019 to September 2020. Patients older than 14 years who underwent to upper gastrointestinal endoscopy were included in the study. **Results:** 179 patients were included in the study. The median age was 48 years, long term use of PPIs was detected in 119 patients(66.5%) with median duration of treatment was 2 years. Abnormal endoscopic findings were more frequently in patients with long term use of PPIs (48.7% vs 25%, p:0.002), especially gastropathy(44.5% vs 20%, p:0.001) and diffuse sessile polyps of gastric fundus(8.4% vs 1.7%,p:0.04). Most of histopathological changes were higher in long term users of PPIs. Diffuse sessile polyps of gastric fundus and fundic gland polyps were found in long term users of PPIs in 9.8%, 7.8% respectively, all of them were in negative helicobacter pylori patients. Long term use of PPIs was associated with an increased risk of dilation of fundic glands(OR:2.6[2.03-3.4],p:0.02),intestinal metaplasia (OR:3.8[0.8-7.6],p:0.001),parietal cell hyperplasia(OR:2.7[2.1- 3.6],p:0.02), and diffuse sessile polyps in gastric fundus(OR:1.9[0.3-3.1],p:0.04). **Conclusion:** Long term use of PPIs was associated with significant endoscopic and histopathologic changes of gastric mucosa, and further studies are required to establish the clinical significance of these changes and the safety of this available drug.

KEYWORDS: Proton pump inhibitor, helicobacter pylori, gastropathy, polyps.

INTRODUCTION

Proton pump inhibitors (PPIs) have been among the most commonly prescribed medications in the world since the first PPIs became available in the 1980s.[1,2] Recently, PPIs have been used widely as the first line treatment for acid related diseases such as gastroesophageal reflux disease (GERD) and gastric ulcers.[3] Although PPIs are generally considered safe, recent data have demonstrated various adverse effects associated with long term use of PPIs.[4] Apart from the systemic adverse effects, there are also concerns on the effects of long term use of PPIs on stomach. The use of PPIs is associated with acid suppression. Moreover, PPIs stimulate production of gastrin which is a potent growth factor.[5] It has been reported that long term use of PPIs also induces histopathological changes such as protrusion of parietal cells into the gland lumen and cystic dilation of gastric fundic glands. In addition to the endoscopic features such as polyps and black spots.[6,7] The absence of local studies prompted us to carry out this research to identify the effects associated with long term use of PPIs.

MATERIALS AND METHODS

Study design and data collection

We studied patients older than 14 years who undergoing upper gastrointestinal endoscopy in the department of Gastroenterology in Tishreen University Hospital – Lattakia-Syria from September 2019 to September 2020. Subjects were divided into two groups: group1 included prolonged users of PPIs and group2 included non-users of PPIs or users for short-term (control group).

Demographic data including age, sex, and duration of therapy with PPIs were recorded. Biopsies of lesions(if

present) and from the antrum, body and fundus of gastric were evaluated.

Definitions

Proton pump inhibitors (PPIs): PPIs effectively block gastric acid secretion by irreversibly binding to and inhibiting the hydrogen-potassium ATPase pump that resides on luminal surface of the parietal cell membrane[8]. PPIs users after the initial prescription lasting more than 6 months were considered as long term users.

Statistical Analysis

Statistical analysis was performed by using IBM SPSS version 20. Basic Descriptive statistics included means, standard deviations(SD) Frequency and percentages.

Differences of distribution examined by using chi-square test or Fisher exact test if it need. Multiple logistic regression was used to detect the effects of PPIs on endoscopic and histological findings. Odd ratios were estimated from b coefficients obtained, with respective 95% confidence intervals(CI 95%).

RESULTS

A total of 179 patients who were admitted to the department of Gastroenterology in Tishreen University Hospital –Lattakia-Syria from September 2019 to September 2020, 119 patients (66.5%) were exposed to long term use of PPIs. The median duration of treatment was 2 years (range from7 months to18 years). The baseline characteristics of patients are as given in table(1).

Patients who exposed to PPIs for long time were older(55 vs 40.5,p:0.02). There was a significant difference between two groups regard to endoscopic findings in which gastropathy and diffuse sessile polyps in gastric fundus were higher in group1 in comparison with group2;(44.5% vs 20%,p:0.001) and (8.4% vs 1.7%,p:0.04) respectively.

Histological changes were more frequently in group1 except of hyperplastic Polyps which were found in one case (1.7%) in group2. Helicobacter pylori was identified in 46.7% of patients in group2.

Table (1): Demographic characteristics of the study population by comparison of the two groups.

Variables	Group1 n=119(66.5%)	Group2 n=60(33.5%)	p-value
Age(years)	55 [17-80]	40.5[15-77]	0.02
Sex Male Female	69(58%) 50(42%)	28(46.7%) 32(53.3%)	0.1
PPIs use ,%(N) 6 month-1 year 1-5 years 5-10 years ≥10years	 24(20.2%) 69(58%) 21(17.6%) 5(4.2%)		
Endoscopic findings Normal **Abnormal** • Gastropathy • Absence of gastric fundus folds • Diffuse sessile polyps of gastric fundus • Abrasions • ulcers	 61(51.3%) 58(48.7%) 53(44.5%) 6(5%) 10(8.4%) 3(2.5%) 7(5.9%)	 45(75%) 15(25%) 12(20%) 1(1.7%) 1(1.7%) 4(6.7%) 3(5%)	 0.002 0.001 0.2 0.04 0.1 0.8
Histological findings • Helicobacter pylori • Gastritis (active or inactive) • Focal hyperplasia • Dilation of fundic glands • Lymphocytic infiltration • Focal fibrosis • Parietal cell hyperplasia • Intestinal metaplasia • Atrophic gastritis • Fundic gland polyps • Gastric endocrine cell hyperplasia • Hyperplastic Polyps	 17(14.3%) 99(83.2%) 47(39.5%) 82(68.9%) 25(21%) 13(10.9%) 85(71.4%) 14(11.8%) 3(2.5%) 8(6.7%) 2(1.7%) 0(0%)	 28(46.7%) 33(55%) 3(5%) 8(13.3%) 5(8.3%) 4(6.7%) 9(15%) 2(3.3%) 1(1.7%) 0(0%) 0(0%) 1(1.7%)	 0.0001 0.0001 0.0001 0.0001 0.03 0.3 0.0001 0.04 0.7 0.04 0.3 0.1

As shown below (Table 2), absence of gastric fundus folds abrasions and ulcers were more frequently in prolonged users of PPIs in presence of helicobacter pylori, whereas diffuse sessile polyps in gastric fundus were found 9.8%,all of them were negative for helicobacter pylori. There was a significant difference

between two groups regard to histological findings in which gastritis, lymphocytic infiltration and atrophic gastritis were more frequently in presence helicobacter pylori.

Table 2: Endoscopic and histological findings in prolonged users of PPIs according to the presence of helicobacter pylori.

	Helicobacter pylori Positive(17)	Helicobacter pylori Negative(102)	P-value
Endoscopic findings			
• Gastropathy	11(64.7%)	42(41.2%)	0.07
• Absence of gastric fundus folds	4(23.5%)	2(2%)	0.0001
• Diffuse sessile polyps of gastric fundus	0(0%)	10(9.8%)	0.1
• Abrasions	2(11.8%)	1(1%)	0.009
• ulcers	3(17.6%)	4(3.9%)	0.02
Histological findings			
• Gastritis (active or inactive)	17(100%)	82(80.4%)	0.04
• Focal hyperplasia	7(41.2%)	40(39.2%)	0.8
• Dilation of fundic glands	14(82.4%)	68(66.7%)	0.1
• Lymphocytic infiltration	9(52.9%)	16(15.7%)	0.0001
• Focal fibrosis	1(5.9%)	12(11.8%)	0.4
• Parietal cell hyperplasia	15(88.2%)	70(68.6%)	0.09
• Intestinal metaplasia	1(5.9%)	13(12.7%)	0.4
• Atrophic gastritis	3(17.6%)	0(0%)	0.002
• Fundic gland polyps	0(0%)	8(7.8%)	0.2
• Gastric endocrine cell hyperplasia	0(0%)	2(1.9%)	0.6

Long term use of PPIs was associated significantly with an increased risk of dilation of fundic glands, intestinal metaplasia, parietal cell hyperplasia, and diffuse sessile polyps in gastric fundus, Table(3) which were represented in Figure(1).

Table (3): Effects of long term use of PPIs on endoscopic and histological findings in the study population by multiple logistic regression.

	OR	Confidence interval (95%)	p-value
Dilation of fundic glands	2.6	[2.03-3.4]	0.02
Intestinal metaplasia	3.8	[0.8-7.6]	0.001
Parietal cell hyperplasia	2.7	[2.1—3.6]	0.02
Diffuse sessile polyps of gastric fundus	1.9	[0.3-3.1]	0.04

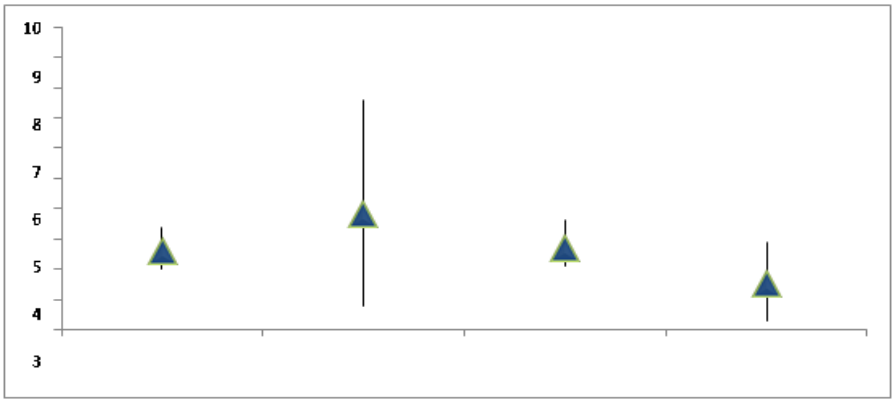

Figure (1): Odds ratios for dilation of fundic glands, intestinal metaplasia, parietal cell hyperplasia, and diffuse sessile polyps in gastric fundus in patients using PPIs for long time

DISCUSSION

This analytical study has demonstrated that abnormal endoscopic findings were more frequently in long term users of PPIs especially gastropathy and diffuse sessile polyps in gastric fundus. As well as histological changes were higher in long term users of PPIs. Our data found higher prevalence of diffuse sessile polyps in gastric fundus and fundic glands polyps in the helicobacter pylori negative patients after long term use of PPIs. Long

term PPIs use was associated with an increased risk of dilation of fundic glands, intestinal metaplasia, parietal cell hyperplasia and diffuse sessile polyps in gastric fundus.

The consequences of long term use of PPIs remains controversial and may be explained as follows: PPIs raise the level of the peptide hormone gastrin, as a result of the homoeostatic response of antral cells, to the reduced acidity of gastric juice.

Gastrin exerts trophic effects on the entire gastrointestinal tract tissue including on both parietal and enterochromaffin-like cells distributed throughout the oxyntic mucosa.[9,10,11]

In comparison with the previous studies, Jalving *et al*(2006) found that long term PPIs use is associated with an up to fourfold increase in the risk of fundic gland polyps(OR:2.2,95% CI:1.3-3.8).[12]

Soumana *et al* (2015) showed in study included 300 patients that use of PPIs increases the incidence of intestinal metaplasia (6.5% vs 1.4%,p:0.023).[13]

Umesh et al (1998) demonstrated that long term use of PPIs may be associated with the presence of gastric fundic gland polyps and hyperplastic polyps.[14]

Zhong et al (2016) found in study included 1465 patients that long term use of PPIs is associated with increased rates of gastric atrophy (OR:1.55,95% CI:1-2.41.[15]

CONCLUSION

Identifying drug-related changes in histological features is important in determining long-term therapeutic safety.

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