Original Research Article

Study of helicobacter pylori negative, non-steroidal anti-inflammatory drug-negative peptic ulcers in a tertiary care center

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Abstract

Background: H. pylori, aspirin, and other non-steroidal anti-inflammatory drugs (NSAIDs) comprise the causes of a large proportion of peptic ulcers. H. pylori-negative, NSAID-negative, and aspirin-negative peptic ulcer disease, are increasing nowadays. While this rise in H. pylori-negative, NSAID-negative ulcer rates reflects a relative increase accompanying a decline in H. pylori-positive ulcers due to the increased use of bacterial elimination therapy or decline of H. pylori infection rate among background healthy population, yearly data also suggest that the actual number of such ulcer patients is increasing. Present study was aimed to study Helicobacter pylori negative, non-steroidal anti-inflammatory drug-negative peptic ulcers at our tertiary care center. **Material and Methods:** Present prospective, observational study was conducted department of Gastroenterology in patients more than 18 years age with at least one site of active gastric or duodenal ulcer detected during endoscopy**. Results:** After applying inclusion and exclusion criteria, 260 patients diagnosed with peptic ulcer disease were considered for present study. Men (68 %) outnumbered women (32 %). Male to female ratio was 2.1 :1. Most common age group was 41-50 years (37 %) followed by 51-60 years (26 %). Mean age was 51 ± 13.9 years in present study. We noted smoking (18%), alcohol abuse (15%), opioid abuser (2%) in present study. In present study incidence of duodenal ulcers (61 %) was more than gastric ulcers (39 %). Compared to urea breath test, rapid urease test had a sensitivity of 89.1% and a specificity of 78.9%. 169 (65 %) patients tested positive by at least one of the tests and were considered to be infected with H. pylori. 91 (35 %) patients with rapid urease test (RUT) and urea breath test (UBT) negative, 37 (41%) had gastric ulcer and 54 (59%) had duodenal ulcer (p-0.041, statistically significant). Patients with both rapid urease test (RUT) and urea breath test (UBT) test negative were comparable in terms age, gender, and presence of risk factors, like smoking and alcoholism with those who tested positive with either rapid urease test (RUT) and/or urea breath test (UBT). **Conclusion:** Increasing incidence of H. pylori-negative, NSAID-negative, and aspirin-negative peptic ulcer disease is noted as compared to past.

Key Words: peptic ulcer disease, Helicobacter pylori; Non-steroidal anti-inflammatory drugs, Helicobacter pylori negative.

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INTRODUCTION

Peptic ulcer is an acid-induced lesion of the digestive tract that is usually located in the stomach or proximal duodenum, and is characterized by denuded mucosa with the defect extending into the submucosa or muscularis propria.[1] The estimated prevalence of peptic ulcer disease in the general population is 5–10%[2]. H. pylori, aspirin, and other non-steroidal anti-inflammatory drugs (NSAIDs) comprise the causes of a large proportion of peptic ulcers. Other causes include Zollinger-Ellison syndrome, Crohn's disease, and viral infections such as cytomegalovirus and herpes, alcohol and tobacco consumption[3]. Although many people who use NSAIDs or aspirin have concurrent H. pylori infection, their interaction in the pathogenesis of peptic ulcer disease remains controversial. A meta-analysis of observational studies resulted in a conclusion that NSAIDs, aspirin use,

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and H. pylori infection increase the risk of peptic ulcer disease independently[4]. H. pylori-negative, NSAID-negative, and aspirin-negative peptic ulcer disease, are increasing nowadays. While this rise in H. pylori-negative, NSAID-negative ulcer rates reflects a relative increase accompanying a decline in H. pylori-positive ulcers due to the increased use of bacterial elimination therapy or decline of H. pylori infection rate among background healthy population, yearly data also suggest that the actual number of such ulcer patients is increasing[5]. H. pylori-negative, NSAID-negative are caused by the imbalance between factors that contribute to mucosal integrity and aggressive insults, but the pathogenic mechanisms behind the development of idiopathic peptic ulcer are still unknown. Present study was aimed to study Helicobacter pylori negative, non-steroidal anti-inflammatory drug-negative peptic ulcers at our tertiary care center.

MATERIAL AND METHODS

Present prospective, observational study was conducted department of Gastroenterology, MLN Medical College. Study duration was 6 months (April 2019 to September 2019). We have taken Institutional ethical committee permission for present study.

Inclusion criteria - Age more than 18 years with at least one site of active gastric or duodenal ulcer (active mucosal lesion with or without scarring, with observable depth and longest diameter of ≥0.3 cm as measured by open biopsy forceps).detected during endoscopy.

Exclusion criteria - Pregnant females, patients who had consumed NSAID, proton pump inhibitors (PPIs), H2-receptor antagonists, bismuth-containing cytoprotective agents, or antibiotics within four weeks prior to entry in the study were excluded. Other exclusion criteria included on-going breast-feeding, presence of underlying malignancy, recent history of GI bleed (<6 months), past history of peptic perforation, pyloric stenosis or any gastric surgery, and inability to give informed consent.

Written informed consent was taken from patients for participation in present study. Demographic, history (medical, family, dietary), clinical details (duration of disease, complications) were collected at the time of participation in present study. A thorough physical examination was done. All relevant laboratory, clinical records, drug intake were reviewed. During endoscopy, one gastric antral biopsy was obtained for rapid urease test (RUT). The tests were read at room temperature after four hours. Patients were subjected to a urea breath test (UBT). After an overnight fast, patients swallowed one capsule of containing 1 μCi 14Clabelled urea with 200 mL of water. After 10 min, the patients exhaled into Breath Card which was then inserted into the analyzer. The results were obtained on-site and expressed as positive or negative. A patient was considered to be H. pylori-positive if either RUT or urea breath test (UBT), or both were positive. Cases who tested negative for both the tests were considered H. pylori-negative. Serum gastrin was measured for all patients included in the study by chemiluminescent immunoassay. All data was collected in Microsoft Excel sheet and analysed.

RESULTS

During study period total 462 gastroscopies were done at our hospital. After applying inclusion and exclusion criteria, 260 patients diagnosed with peptic ulcer disease were considered for present study. Men (68 %) outnumbered women (32 %). Male to female ratio was 2.1 :1. Most common age group was 41-50 years (37 %) followed by 51-60 years (26 %). Mean age was 51 ± 13.9 years in present study. We noted smoking (18%), alcohol abuse (15%), opioid abuser (2%) in present study. In present study incidence of duodenal ulcers (61 %) was more than gastric ulcers (39 %). We noted no correlation between gender and location of ulcer. Serum gastrin levels were measured in all patients, levels were comparable in both the groups.

Table 1: Clinical and demographic features of the patients with peptic ulcer disease

Characteristic	Frequency	N (%)
Total number of patients	260	
Men	176	68%
Women	84	32%
Age (mean in years)	51 ± 13.9	
Smoking	47	18%
Alcohol abuse	38	15%
Opioid Abusers	6	2%
Ulcer location		
DU (duodenal ulcer)	158	61%
GU (gastric ulcer)	102	39%

NSAID-non-steroidal anti-inflammatory drug

We noted 91 (35 %) patients with rapid urease test (RUT) and urea breath test (UBT) negative, while 30 (12 %) patients were isolated RUT positive, 21 (8 %) patients were isolated UBT positive and 118 (45 %) patients were both rapid urease test (RUT) and urea breath test (UBT) positive. Out of 102 patients with gastric ulcer, 37 (36 %) patients were rapid urease test (RUT) and urea breath test (UBT) negative, while 8 (8 %) patients were isolated RUT positive, 9 (9 %) patients were isolated UBT positive and 48 (47 %) patients were both rapid urease test (RUT) and urea breath test (UBT) positive. Out of 158 patients with gastric ulcer, 54 (34 %) patients were rapid urease test (RUT) and urea breath test (UBT) negative, while 22 (14 %) patients were isolated RUT positive, 12 (8 %) patients were isolated UBT positive and 70 (44 %) patients were both rapid urease test (RUT) and urea breath test (UBT) positive. Compared to urea breath test, rapid urease test had a sensitivity of 89.1% and a specificity of 78.9%. 169 (65 %) patients tested positive by at least one of the tests and were considered to be infected with H. pylori. 91 (35 %) patients with rapid urease test (RUT) and urea breath test (UBT) negative, 37 (41%) had gastric ulcer and 54 (59%) had duodenal ulcer (p-0.041, statistically significant). Patients with both rapid urease test (RUT) and urea breath test (UBT) test negative were comparable in terms age, gender, and presence of risk factors, like smoking and alcoholism with those who tested positive with either rapid urease test (RUT) and/or urea breath test (UBT).

Table 2: Results of rapid urease test and urea breath test in the study population

Result		Total (n=260)	Gastric ulcer (n=102)	Duodenal ulcer (n=158)	p-value
Both RUT and UBT negative		91 (35 %)	37 (36 %)	54 (34%)	Statistically Significant
RUT positive and/or UBT positive	Isolated RUT positive	30 (12 %)	8 (8 %)	22 (14 %)	Not Significant
	Isolated UBT positive	21 (8 %)	9 (9 %)	12 (8 %)	Not Significant
	Both tests positive	118 (45 %)	48 (47 %)	70 (44 %)	Not Significant

RUT - rapid urease test, UBT- urea breath test

DISCUSSION

Traditionally, mucosal disruption in patients with the acid peptic disease is considered to be a result of a hypersecretory acidic environment together with dietary factors or stress. Risk factors for developing peptic ulcer include H. pylori infection, alcohol and tobacco consumption, non-steroidal anti-inflammatory drugs (NSAIDs) use, and Zollinger–Ellison syndrome[6]. The main risk factors for both gastric and duodenal ulcers are H. pylori infection and NSAID use[6]. Many factors contribute to the development of PUD, of which environmental factors such as psychosocial conditions and stress are the most outstanding[7]. Stress is an acute hazard/risk to homeostasis that excites an allostatic or adaptive response. Stress affects the function of the gastrointestinal tract either in short or long-term impacts. Stress due to serious health problems such as those requiring treatment in an intensive care unit is well described as a cause of peptic ulcers, which are termed stress ulcers[8]. While chronic life stress was once believed to be the main cause of ulcers this is no longer the case. It is, however, still occasionally believed to play a role.54 Dietary factors such as spice consumption, were hypothesized to cause ulcers until late in the 20th century, but have been shown to be of relatively minor importance9. Caffeine and coffee, and also commonly thought to cause or exacerbate ulcers, appear to have little effect. Skipping of meals allows gastric acid to directly act on surface mucosa of the stomach causing irritation which ultimately leads to gastric ulcers. Gastric ulcers cause abdominal pain which aggravate with meals[10]. The possible underlying etiologies of H pylori–negative idiopathic ulcers include other medications such as potassium supplements, calcium channel blockers, and antidepressants, infections such as cytomegalovirus, inflammatory bowel disease (IBD), chronic mesenteric ischemia, and Zollinger–Ellison syndrome[11]. A test-and-treat strategy for H. pylori infection has been adopted as first-line management for patients with PUD, while a screen-and-treat strategy for H. pylori infection in the asymptomatic population has been considered as an effective approach to decrease future risk of gastric cancer[12,13]. Bacterial elimination therapy is often effective for preventing the recurrence of H. pylori-positive ulcers and does not require subsequent maintenance therapy with acid-suppressive agents. In NSAID-induced ulcers, changing therapy to COX-2-selective NSAIDs or other alternative medications that do not cause as much damage to the gastrointestinal mucosa can be expected to suppress recurrences. However, for idiopathic ulcers, although acid-suppressive agents can produce temporary relief, they are not an effective preventative measure against recurrence. It has been shown that recurrence rates are high when patients remain unmedicated after such temporary cures. A meta-analysis has revealed the following pooled sensitivity and specificity for different methods: rapid urease test 0.67 and 0.93; histology 0.70 and 0.90; culture 0.45 and 0.98; urea breath test 0.93 and 0.92; stool antigen test 0.87 and 0.70; and serology 0.88 and 0.69, respectively, which clearly demonstrates that each of the different tests has its own limitations, and a single negative test does not exclude H. pylori infection[15]. We noted 35 % of H. pylori-negative, NSAID-negative, and aspirin-negative peptic ulcer disease in present study.

In a study by Xia and colleagues the prevalence of 40% in Australia16. Also, Goenka and co-workers reported a similar result in India in 201117. But a few studies from Italy and Japan show that the frequency is still low in these societies[18,19]. We noted urea breath test when compared to rapid urease test had a sensitivity of 89.1% and a specificity of 78.9%. 91 (35 %) patients with rapid urease test (RUT) and urea breath test (UBT) negative, 37 (41%) had gastric ulcer and 54 (59%) had duodenal ulcer (p-0.041, statistically significant). Preliminary data suggest that patients with H pylori–negative idiopathic ulcers have a poor long-term outcome. In a prospective cohort study with H pylori–negative idiopathic bleeding ulcers, they noted the incidence rate of recurrent ulcer bleeding as 3.8 per 100 person-years, compared with 0.4 per 100 person-years in patients with prior H pylori bleeding ulcers. Patients with H pylori–negative idiopathic bleeding ulcers also had significantly higher mortality (14.9 per 100 person-years) than patients with H pylori bleeding ulcers (5.4 per 100 person-years)[20]. The long-term management of H pylori–negative idiopathic ulcers is poorly defined because its pathophysiology is largely unknown. Early studies suggested that some of these patients had increased gastrin and acid hypersecretion. However, these abnormalities might be related to rebound acid secretion after withdrawal of PPIs[21].

CONCLUSION

Increasing incidence of H. pylori-negative, NSAID-negative, and aspirin-negative peptic ulcer disease is noted as compared to past. During diagnosis idiopathic ulcers (H. pylori-negative, NSAID-negative, and aspirin-negative) should be a differential diagnosis in ulcers not responding to routine management.

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