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ORIGINAL ARTICLE

Helicobacter pylori negative, non-steroidal anti-inflammatory drug-negative peptic ulcers in India

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Abstract
Introduction The past decade has witnessed a global rise in the prevalence of peptic ulcer disease which is unrelated to non-steroidal anti-inflammatory drugs (NSAIDs) or *Helicobacter pylori* infection. Although initially recognized in the West, this disease is being increasingly recognized in the Asian population. The higher risk of bleeding and ulcer recurrence in this subgroup of patients highlights the clinical importance of analyzing the changing trends of peptic ulcer disease in developing countries.
Aims To assess the proportion of non-NSAID, non-*H. pylori* peptic ulcer disease in an Indian cohort of patients with peptic ulcer disease managed at a tertiary care center; and to compare the gastric and duodenal ulcer subgroups in these patients.
Methods Patients diagnosed with peptic ulcer disease were screened for a history of NSAID use and those with a negative history were tested for *H. pylori* using a combination of rapid urease test (RUT) and ^{14}C-urea breath test (UBT). Only those cases which tested negative for both the tests were considered '*H. pylori*-negative'. Serum gastrin was measured in all patients included in the study.
Results Seventy-four gastric ulcer (GU) and 54 duodenal ulcer (DU) patients with no history of NSAID use were enrolled. Of these, 36 GU (45.9%) and 16 DU (29.6%) patients were *H. pylori*-negative. The proportion of non-NSAID non-*H. pylori* gastric ulcers was significantly higher than duodenal ulcers ($p<0.05$). However, patients who tested negative for *H. pylori* did not differ significantly from those who tested positive with regard to age, gender, serum gastrin level, and presence of risk factors, like smoking and alcoholism.
Conclusion The current study indicates existence of high proportion of non-NSAID, non-*H. pylori* peptic ulcer disease in Indian patients.

Keywords *Helicobacter pylori* · Idiopathic · NSAID · Ulcer

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Introduction

Helicobacter pylori (*H. pylori*) infection and non-steroidal anti-inflammatory drugs (NSAIDs) have for long been considered to be the major etiological factors in the causation of peptic ulcer disease. However, recent years have witnessed a paradigm shift in the epidemiology of peptic ulcer disease. A review of medical literature suggests that the proportion of *H. pylori* negative peptic ulcer disease has been increasing in developed countries [1]. Recent North American data suggests that up to 50% of ulcers are *H. pylori* negative [2]. *H. pylori* infection is more prevalent in developing countries, with some regions recording background prevalence close to 100%. However, recent reports from different parts of Asia have shown a declining trend for *H. pylori*-associated ulcers [3, 4]. The parallel forces of effective eradication and improvement in hygiene and living conditions have possibly contributed to this decline. The proportion of *H. pylori*-negative, NSAID-negative ulcers has not been previously documented in India. Since *H. pylori*-negative ulcers have been shown to have a higher incidence of mortality and recurrent bleeding, documenting the proportion of such cases is important [5]. In this study, we have estimated the

proportion of *H. pylori*-negative NSAID negative peptic ulcer cases and have also compared the characteristics of patients with gastric ulcer (GU) and duodenal ulcer (DU).

Methods

Patient selection

For this single-center cross-sectional study, we recruited patients aged more than 18 years old, with at least one site of active gastric or duodenal ulcer detected during endoscopy. An ulcer was defined as an active mucosal lesion with or without scarring, with observable depth and longest diameter of ≥0.3 cm as measured by open biopsy forceps [6]. Female subjects were included only if they either had no child-bearing potential (e.g., surgically sterile, post-menopausal), or had a negative urine pregnancy test. History of previous gastrointestinal (GI) disorders and drug intake were recorded. Patients who had consumed NSAID, proton pump inhibitors (PPIs), H_2-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.

Patients satisfying the above mentioned criteria were included during the study period from January 2008 to June 2009. The study was approved by the institutional clinical research review committee of our hospital. Demographic, clinical, and relevant laboratory data were collected after obtaining informed consent from each patient included in the study.

Diagnosis of *Helicobacter pylori*

During endoscopy, one gastric antral biopsy was obtained for rapid urease test (RUT) (Pylotest™, Halifax Research Laboratory, Kolkata). The tests were read at room temperature after four hours.

All patients were subsequently subjected to a ^{14}C-urea breath test, performed in accordance with the manufacturer's recommendations (Heliprobe, Wedholm Medical, Kibion, Sweden). After an overnight fast, patients swallowed one capsule of HeliCap™ containing 1 μCi ^{14}C-labelled urea with 200 mL of water. After 10 min, the patients exhaled into BreathCard™ which was then inserted into the Heliprobe$^{(R)}$ analyzer [7]. 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 (Immulite 2000, Siemens, Deerfield, USA).

Statistical analysis

The χ^2 test was used for testing association between qualitative variables and the 't' test was used for quantitative variables. Sensitivity and specificity of the RUT were calculated against the ^{14}C-urea breath test. Data were processed and analyzed with SPSS (Statistical Package for the Social Sciences) version 12.0. A value of $p<0.05$ was considered significant.

Results

Of the 192 patients diagnosed with peptic ulcer disease during the study period, 128 (mean age 42.3 [range 18–72] years; 108 men) matched our inclusion criteria. Sixty-four patients were excluded because of various criteria (NSAID intake 14, PPI and/or H_2 receptor antagonist 32, recent GI bleeding 8, gastric surgery 6, absence of consent 2, underlying malignancy 2). Seventy-four patients (57.8%) had gastric and 54 (42.2%) had duodenal ulcers. There was no correlation between gender and location of ulcer. Serum gastrin levels were comparable in both the groups.

Table 1 shows the results of RUT and ^{14}C-UBT in patients. Out of the 128 patients, 69 (54%) and 66 (51.6%) patients tested positive for RUT and UBT, respectively; while, 12 (17.4%) patients with a positive RUT tested negative by UBT and 9 (15.2%) patients with a negative RUT tested positive by UBT. Compared to UBT, RUT had a sensitivity of 86.4% and a specificity of 80.6%. Seventy-eight (60.9%) patients tested positive by at least one of the tests and were considered to be infected with *H. pylori*. Of the 50 (39.1%) patients who were negative for *H. pylori*, 34 (68%) had GU and 16 (32%) had duodenal ulcer ($p<0.05$). Patients who tested negative for *H. pylori* did not differ from those who tested positive with regard to age, gender, and presence of risk factors, like smoking and alcoholism (Table 2).

Discussion

Helicobacter pylori infection and the use of traditional non-steroidal NSAID have for long been considered as important factors in the pathogenesis of peptic ulcer disease. Recent reports however, show a significant difference in the proportion of *H. pylori*-negative ulcers across continents

Table 1 Outcome of rapid urease test and urea breath test in the study population

		Total (n=128)	Gastric ulcer (n=74)	Duodenal ulcer (n=54)	p-value
Both RUT and UBT negative		50 (39.1)	34 (45.9)	16 (29.6)	0.03
RUT positive and/or UBT positive	Isolated RUT positive	12 (9.4)	6 (8.1)	6 (11.1)	NS
	Isolated UBT positive	9 (7)	4 (5.4)	5 (9.2)	NS
	Both tests positive	57 (44.5)	30 (40.5)	27 (50)	NS

Values are as n (%).

RUT: rapid urease test; *UBT*: urea breath test

(Table 3) [8–17]. Over the past decade, the etiological role of *H. pylori* as the primary causative factor in DU has been questioned [18, 19]. A number of recent studies have documented an increase in *H. pylori*-negative peptic ulcer disease [20]. A retrospective study by Jyotheeswaran et al. from the USA reported an *H. pylori* negativity rate of 61% after exclusion of NSAID use in DU patients [2]. Further evidence of this low prevalence of *H. pylori* comes from six large trials done in the USA involving more than two thousand patients which found as many as 27% DU patients to be *H. pylori* negative [17, 21]. On the contrary, studies from Europe reflect a much lower prevalence of *H.pylori*-negative peptic ulcers. A study from Northern Italy reported a prevalence of only 8% [22]. Arroyo et al. from Spain concluded that peptic ulcer disease was still highly associated with *H. pylori* infection in Southern Europe, and only 1.6% of all duodenal ulcers and 4.1% of all GUs were found to be negative for both *H. pylori* and NSAIDs [1]. Reports from different parts of Asia show wide variation. The reported prevalence of *H. pylori*-negative peptic ulcer ranges from as low as 3% in Japan to as high as 29% in Singapore and Pakistan [14, 23–25]; recent reports from Hong Kong also stress on the changing epidemiology of *H. pylori* in Asia [16].

Recent Indian data show a significant decline in the background prevalence of *H. pylori* with about 45% asymptomatic subjects harboring infection [26]. This downward trend in prevalence is significant because a small decline in the community prevalence of *H. pylori* infection markedly increases the proportion of *H. pylori*-negative ulcers compared to *H. pylori*-positive ulcers, if the total prevalence of peptic ulcer disease in the community remains unchanged. All prior Indian studies looking at the prevalence of *H. pylori* have reported positivity rates of more than 80% in peptic ulcer patients [27, 28]. This study is the first prospective study to report proportion of NSAID-negative *H. pylori*-negative peptic ulcer disease in India. A high proportion of peptic ulcer patients in our study, were negative for *H. pylori*. This not only represents a significant epidemiological shift but carries great clinical importance, since these ulcers are known to be refractory to therapy and possess a relatively high risk of complications [5].

There was no relationship between *H. pylori* negativity and age or gender in our patients. The lack of gender predisposition is in accordance with the previous reports [29]. There are a number of conflicting reports where idiopathic peptic ulcers (*H. pylori* negative, NSAID negative) have been variably attributed to younger and older age groups [23, 30]. Although our study population was relatively young, we did not find any association between idiopathic ulcers and any particular age group. Moreover, conventional risk factors, like smoking and alcohol consumption were not different between *H. pylori*-positive and negative groups.

Defining a diagnostic standard has often proved to be the stumbling block for studies evaluating *H. pylori* prevalence. It is therefore difficult to compare results from different studies using various combinations of diagnostic tests. A possible limitation of our study was that we did not use histology for diagnosis of *H. pylori*. We wanted to evaluate only the current infection with *H. pylori* and hence did not evaluate for antibody against *H. pylori.* Although histopathology and culture for *H. pylori* has been used in previous

Table 2 Distribution of *H. pylori* positive and negative subjects in gastric and duodenal ulcer groups

	Total (n=128)	Gastric ulcer (n=74)		Duodenal ulcer (n=54)	
		HP+ve	HP−ve	HP+ve	HP−ve
Number	128 (100)	40 (54.1)	34 (45.9)	38 (70.4)	16 (29.6)
Median age (years)	39	45	38	38	45
Male	108 (84.4)	33 (82.5)	29 (85.3)	34 (89.5)	12 (75)
Smoking	36 (28.1)	12 (30)	12 (35.3)	9 (23.7)	3 (18.7)
Alcohol	8 (6.2)	2 (5)	4 (11.8)	1 (2.6)	1 (6.2)

Values are as n (%).
HP: *Helicobacter pylori*

p=NS between HP-positive and HP-negative patients in both GU and DU groups

Table 3 Prevalence of *H. pylori*-negative, NSAID-negative ulcers in previously published studies

Study region	Author (Reference)	Year	Total cases	*H. pylori* and NSAID-negative ulcers (%)
Australia	Borody [8]	1991	302 DU	10 (3)
	Borody [9]	1992	115 GU	13 (11)
	Xia [10]	2000	45 GU or DU	17 (38)
Spain	Gisbert [11]	1999	774 DU	6 (1)
	Arroyo [1]	2004	472 DU, 193 GU	8 (2) DU, 25 (13) GU
Denmark	Bytzer [12]	2001	275 DU	22 (8)
Italy	Oderda [13]	2009	47 DU, 23 GU	23 (49) DU, 6 (26) GU
Japan	Nishikawa [14]	2000	398 GU or DU	5 (1)
Hong Kong	Chan [15]	2001	954 GU or DU	40 (4)
	Hung [16]	2005	275 DU, 314 GU, 49 GU+DU	49 (18) DU, 63 (20) GU, 8 (16) DU+GU
USA	Jyotheeswaran [2]	1998	160 DU, 145 GU	56 (35) DU, 50 (35) GU
	Ciociola [17]	1999	2394 DU	657 (27)

DU: Duodenal ulcer; *GU*: Gastric ulcer

studies as a gold standard; sampling error, interobserver variability, increased cost, and diagnostic delay are significant pitfalls associated with it [22, 23]. The Maastricht III consensus report mentions satisfactory diagnostic accuracy (>90%) of the RUT [31]. We aimed to increase this further by excluding patients with recent intake of antisecretory drugs. The same report has also recommended the UBT as the best non-invasive option to establish the diagnosis of *H. pylori* infection with 94% sensitivity and 95% specificity. Since our focus was on documenting *H. pylori* negativity, we chose parallel testing with RUT and ^{14}C-UBT to increase sensitivity albeit at the cost of a small proportion of false positive tests. Serial testing with RUT and ^{14}C-UBT, if applied to our study population, would increase the proportion of *H. pylori*-negative ulcers to 55.5%. Parallel testing effectively achieved our main objective, thereby minimizing the chances of overestimation of *H. pylori*-negative NSAID-negative peptic ulcers.

The etiopathogenesis of non-NSAID non-*H. pylori* ulcer disease is yet to be established. Whether gastric acid hypersecretion is responsible for the development of these ulcers is still controversial [20]. Spurious use of NSAIDs, cyclo-oxygenase-2 inhibitors, aspirin, and other anti-platelet agents have been implicated as a cause of these "idiopathic ulcers". Other rare causes of non-NSAID non-*H. pylori* ulcers include cirrhosis, Crohn's disease, Zollinger-Ellison syndrome, Behcet's disease, ischemia, and infections, such as Cytomegalovirus and *Helicobacter heilmannii* [20]. Although PPIs are currently used for treating these ulcers, data regarding their efficacy is lacking. Non-NSAID non-*H. pylori* ulcers have a five-fold higher risk of recurrence compared to *H. pylori*-positive ulcers treated with eradication therapy [16]. In a seven-year prospective cohort study, the rate of ulcer recurrence and complication was significantly higher in *H. pylori*-negative patients compared to those who were *H. pylori*-positive [32]. In the absence of established treatment protocols, long-term maintenance therapy with PPIs is often continued indefinitely, especially in elderly patients with multiple comorbidities.

Contrary to previous data from India, our study had more gastric ulcers compared to duodenal ulcers. This could be due to referral patterns of hospital and a significant number of patients excluded due to reasons mentioned earlier. Moreover, we have documented in our earlier epidemiological study [33], a changing trend in relative frequency of GU and DU in India with a relatively higher proportion of GU. Of the 50 patients diagnosed with *H. pylori*-negative and NSAID-negative peptic ulcers in our study, the proportion of GUs were greater than duodenal ulcers (34/74 vs. 16/54, $p<0.05$). Previous studies done in Asian population have also shown a trend for higher proportion of non-NSAID, non-*H. pylori* ulcers in the stomach compared to the duodenum, but the difference was not significant [16]. Although our study uncovers a significant trend in the Indian peptic ulcer patients, we were limited by the unavailability of ulcer histology, antibody testing, or tissue cultures for *H. pylori* and lack of follow up, all of which have the potential of yielding valuable information in this growing population of idiopathic ulcers. Other notable limitations of our study were the relatively small number of patients and lack of gastric acid output estimation which would have enabled further characterization of our patients. However, serum gastrin was used as a surrogate marker of gastric acid secretion and the values did not differ significantly among the *H. pylori*-positive and negative subgroups.

To conclude, our study shows that the existence of high proportion of *H. pylori*-negative, NSAID-negative peptic ulcer disease is not confined to developed

countries. A greater proportion of gastric ulcer patients were NSAID-naive and *H. pylori* negative compared to duodenal ulcers.

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