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ORIGINAL PAPER

Has Peptic Ulcer Disease Changed During the Past Ten Years in Korea? A Prospective Multi-center Study

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Abstract *Background* The incidence of *H. pylori*-negative, idiopathic peptic ulcer disease (IPUD) seems to be increasing with the changing trends of PUD and *H. pylori* infection in some developed countries. *Aim* To investigate the changing trend of PUD and the prevalence of *H. pylori* infection during the last decade and the prevalence of IPUD in Korea. *Methods* We prospectively evaluated *H. pylori* infection and the characteristics of PUD in 895 patients with newly diagnosed PUD from September 2004 to February 2005. *Results* The *H. pylori* infection rate in PUD was 72.0% and the proportion of IPUD was 22.2%. The proportion of gastric ulcer (GU) has significantly increased (47.8% vs. 44.3%) and the proportion of duodenal ulcer (DU) has significantly decreased (38.9% vs. 44.9%) compared with ten years ago. The changing trend in the prevalence of *H. pylori* infection in GU and DU showed an increase in GU (66.1% vs. 73.1%, $P = 0.014$) and a decrease in DU (79.3% vs. 68.1%, $P = 0.001$). *Conclusion* Compared with our results of ten years ago, there has been a significant change in the distribution of PUD and in the prevalence of *H. pylori* infection in GU and DU. Patients with IPUD are not uncommon in Korea.

Keywords *Helicobacter pylori* · Idiopathic ulcer · Non-steroidal anti-inflammatory drugs · Peptic ulcer disease

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Introduction

Helicobacter pylori (*H. pylori*) infection has proven to be the major cause of peptic ulcer disease (PUD) [1]. *H. pylori* infection has been found in 73–100% of patients with duodenal ulcers (DU) and 65–100% of patients with gastric ulcers (GU) [2–7]. Because *H. pylori* infection is generally regarded as a causal factor in the pathogenesis of PUD, it has been widely eradicated in Korea, similar to other countries.

There have been some reports showing a recent decreasing trend in the global prevalence of PUD [8–10]. This decline might be due to the decreasing prevalence of *H. pylori* infection [11]. Alternatively, it might be explained by the recent use of cyclo-oxygenase-2 (COX-2) selective non-steroidal anti-inflammatory drugs (NSAIDs), which have also diminished gastroduodenal lesions.

However, NSAIDs and aspirin remain among the most widely used drugs for various indications such as pain, inflammation, and the prevention of cardiovascular and cerebrovascular events [12]. NSAID or aspirin use increases with age and 10–20% of the elderly have a

current or recent prescription [12]. NSAID or aspirin use is regarded as a major risk factor in non-*H. pylori* associated PUD, especially GU [13, 14]. Therefore, study of the changing trend in the prevalence of *H. pylori* infection and NSAID-associated PUD is an important clinical aspect.

While, overall, PUD appears to be declining, the proportion of *H. pylori*-negative, idiopathic peptic ulcer disease (IPUD) may be increasing. Studies in the United States have shown that 11–44% of PUD is not associated with *H. pylori* infection or the use of NSAIDs. Therefore, these studies suggest that the role of *H. pylori* infection in PUD might be overestimated [15–17]. However, *H. pylori*-negative IPUD is thought to be rare in Japan and Europe [18–20] contrary to reports from the United States.

The objectives of this study were to evaluate changing trends in the prevalence of *H. pylori* infection in patients with PUD during the last decade and to determine the prevalence and clinical characteristics of *H. pylori*-negative IPUD in Korea.

Methods

Patients

This prospective study was conducted at Hallym University Medical Center. We prospectively enrolled a total of 895 consecutive patients from five hospitals of the Hallym University Medical Center from September 2004 to February 2005. All enrolled patients received an upper gastrointestinal endoscopic examination and were diagnosed as PUD. As in the design of our previous study [21], patients who had taken antibiotics, a bismuth compound, or a proton-pump inhibitor within four weeks prior to the upper gastrointestinal endoscopy were not considered for enrollment. Diagnosis of gastric cancer had to be histologically excluded from the study.

Users of NSAIDs or aspirin were identified by taking a careful history and reviewing medical records, especially for patients with underlying diseases such as cardiovascular disease or arthritis. IPUD was defined as an ulcer without documented *H. pylori* infection or prior exposure to aspirin or NSAIDs within four weeks before endoscopic examination. The prevalence of *H. pylori* infection and the distribution of PUD were compared with those in our previous study performed during a similar period ten years ago [21].

This study was approved by the Clinical Trial Ethics Committee of the Hallym University College of Medicine. All patients provided written informed consent.

Diagnostic methods for *H. pylori* infection

Two biopsy specimens were taken, one each from the antrum and the corpus. *H. pylori* infection was assessed by the rapid urease test and histology using Giemsa stain. Patients were considered to be negative for *H. pylori* infection if both the histological examination and the rapid urease test were negative. Patients were considered as positive for *H. pylori* if either test was positive.

Statistical analysis

SPSS (Chicago, IL, USA) software version 11.0 for Windows was used for statistical analysis. The patients' baseline characteristics were presented as descriptive data. We used the Student *t*-test to compare means, the Mann–Whitney *U*-test to compare medians, and the Pearson χ^2 test to compare categorical data. $P < .05$ was considered statistically significant.

Results

Between September 2004 and February 2005, 895 patients with newly diagnosed PUD were enrolled. There were 586 men and 309 women with a mean age of 50.7 years. Four-hundred and twenty-eight patients (47.8%) were found to have GU, 348 (38.9%) had DU, and 119 (13.3%) had concurrent gastric and duodenal ulcers (GUDU). Clinical and demographic characteristics of the patients are summarized in Table 1.

Table 1 Clinical and demographic characteristics

Characteristics	*n* (%)
Total number of patients	895 (100)
Men	586 (65.5)
Women	309 (34.5)
Age (years, mean ± SD)	50.7 ± 15.5
NSAID or aspirin use	116 (13.0)
NSAID	59 (6.6)
Aspirin	62 (6.9)
Smoking	293 (32.7)
Alcohol	369 (41.2)
Location of peptic ulcer	
GU	428 (47.8)
DU	348 (38.9)
GU and DU	119 (13.3)
Concurrent ulcer-related complication	
Bleeding	118 (13.2)
Obstruction	9 (1.0)
Perforation	1 (0.1)

SD, standard deviation; NSAID, non-steroidal anti-inflammatory drug; GU, gastric ulcer; DU, duodenal ulcer

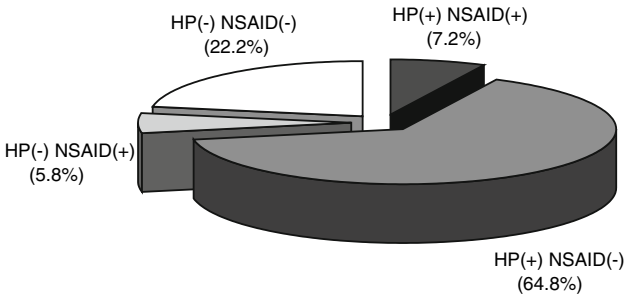

Fig. 1 Proportion of *H. pylori* infection and the use of NSAIDs/aspirin in peptic ulcer disease; *HP*, *Helicobacter pylori*; *NSAID*, non-steroidal anti-inflammatory drug

The *H. pylori* infection rate in PUD was 72.0% and the proportion of IPUD was 22.2% (Fig. 1). The proportion of ulcers associated with NSAIDs or aspirin, regardless of *H. pylori* infection, was 13.0%. Table 2 shows results from comparison of the clinical features of patients with GU and DU. Patients with GU were significantly older ($P = 0.001$) and had more aspirin use ($P = 0.010$) than those with DU. Clinical features of IPUD were compared with those of PUD associated with *H. pylori* or NSAID use (Table 3). There were no significant differences between the clinical characteristics in GU. The DU patients with *H. pylori* infection or NSAID use had significantly more alcohol consumption than those with idiopathic DU ($P = 0.018$). In the comparison of the results between idiopathic GU and DU, idiopathic GU patients had more bleeding complications than idiopathic DU patients ($P = 0.049$).

The changing trend in the distribution of PUD and the prevalence of *H. pylori* infection were compared with those of our previous report from ten years ago (Table 4). The changing trend in the prevalence of *H. pylori* infection during the past ten years in GU and DU showed converse findings—an increase in GU (66.1% vs. 73.1%, $P = 0.014$) and a decrease in DU (79.3% vs. 68.1%, $P = 0.001$). Among patients with PUD, the proportion of GU (47.8%, 428/895, $P = 0.018$) has significantly increased (44.3%, 457/1031) and the proportion of DU (38.9%, 348/895, $P = 0.015$) has significantly decreased (44.9%, 463/1031) compared with ten years ago.

Discussion

Although *H. pylori* infection is the main cause of PUD [4], the prevalence of *H. pylori* infection is changing and, according to some reports, the proportion of ulcers not associated with *H. pylori* infection seems to be increasing [8–10, 22, 23]. Compared with our results ten years ago, there has been a significant change in the prevalence of *H.*

Table 2 Comparison of the clinical characteristics of patients with gastric ulcer and duodenal ulcer

Parameter	GU (%) ($n = 428$)	DU (%) ($n = 348$)	*P*-value
Age (years, mean ± SD)	54.6 ± 14.1	47.1 ± 14.2	0.001
Male	265 (61.9)	230 (66.1)	0.229
Smoking	123 (28.7)	122 (35.1)	0.060
Alcohol	162 (37.8)	146 (41.9)	0.245
NSAID	28 (6.5)	21 (6.0)	0.772
Aspirin	37 (8.6)	14 (4.0)	0.010
H. pylori infection	313 (73.1)	237 (68.1)	0.125
Idiopathic ulcer	90 (21.0)	92 (26.4)	0.077
Bleeding	59 (13.8)	36 (10.3)	0.219
Obstruction	2 (0.5)	6 (1.7)	0.149

SD, standard deviation; NSAID, non-steroidal anti-inflammatory drug; GU, gastric ulcer; DU, duodenal ulcer

Table 3 Comparison of the clinical characteristics between idiopathic peptic ulcer disease and peptic ulcer disease associated with *H. pylori* or NSAID use

Parameter	GUHP or NSAID associated ($n = 338$) (%)	Idiopathic ($n = 90$) (%)	*P*-value	DUHP or NSAID associated ($n = 256$) (%)	Idiopathic ($n = 92$) (%)	*P*-value
Age (years, mean ± SD)	54.5 ± 13.5	54.9 ± 16.3	0.831	46.3 ± 14.0	49.1 ± 14.7	0.110
Male	217 (64.2)	48 (53.3)	0.059	173 (67.6)	57 (61.9)	0.329
Smoking	101 (29.9)	22 (24.4)	0.311	97 (37.9)	25 (27.2)	0.065
Alcohol	124 (36.7)	38 (42.2)	0.336	117 (45.8)	29 (31.5)	0.018
Bleeding	44 (13.0)	15 (16.7)	0.087	30 (11.7)	6 (6.5)	0.160
Obstruction	1 (0.2)	1 (1.1)	0.371	6 (2.3)	0 (0)	0.347

SD, standard deviation; NSAID, non-steroidal anti-inflammatory drug; GU, gastric ulcer; DU, duodenal ulcer; HP, *H. pylori*

Table 4 Changes of the distribution of peptic ulcer disease and the prevalence of *Helicobacter pylori* infection in ten years

Year	Distribution of PUD			Prevalence of *H. pylori* infection		
	1994–1995	2004–2005	*P*-value	1994–1995	2004–2005	*P*-value
GU	457/1031 (44.3%)	428/895 (47.8%)	0.018	302/457 (66.1%)	313/428 (73.1%)	0.014
DU	463/1031 (44.9%)	348/895 (38.9%)	0.015	367/463 (79.3%)	237/348 (68.1%)	0.001
GUDU	111/1031 (10.7%)	119/895 (13.3%)	0.125	79/111 (71.1%)	94/119 (78.9%)	0.111

GU, gastric ulcer; DU, duodenal ulcer ; PUD, peptic ulcer disease

pylori infection in GU and DU. Unfortunately, as we have no Korean data about the changing pattern of *H. pylori* infection, we cannot compare the prevalence of *H. pylori* infection in the Korean population.

The prevalence of *H. pylori* infection in GU and DU showed increasing and decreasing trends, respectively, compared with our results from ten years ago. It has been shown in several studies that DU is more commonly related to *H. pylori* infection than GU [4–6]. Widespread eradication of *H. pylori* might have a more profound effect on the prevalence of DU than GU. Although a decrease in the prevalence of *H. pylori* infection in PUD was expected, the fact that we found no significant change in the overall prevalence of *H. pylori* infection in PUD in the past ten years might reflect that the attributable risk of *H. pylori* infection in PUD was not affected by the prevalence of *H. pylori* infection in the general population [24]. It would be more reasonable to compare the prevalence of *H. pylori* infection in subgroups such as GU and DU.

The reason for an increase in the prevalence of GU compared with ten years ago may be that ulcers associated with NSAIDs or aspirin are increasing. In this study, GU patients were older and were more likely to use aspirin than DU patients. Aspirin has been widely used as an antithrombotic drug for prevention of cardiovascular and cerebrovascular events. Even low-dose aspirin, generally defined as 75–325 mg per day, is associated with a significant risk of developing serious gastrointestinal complications, such as bleeding [25, 26]. We suggest that aspirin will begin to have a more important role as the underlying cause of PUD, especially in GU.

The prevalence of IPUD differs from country to country. Several North American studies showed that 11–44% of patients had PUD without *H. pylori* infection or NSAID use [15–17]. In the Japanese population, the incidence of IPUD was very low (1.3%) [18]. The incidence of idiopathic bleeding ulcers was found to be increasing in a recent report from Hong Kong [22]. The prevalence of IPUD in this study was 22.2%, which was similar to results obtained in North America. Unfortunately, we could not compare our present results with our previous results ten years ago because we did not investigate the prevalence of IPUD ten years ago. IPUD was more frequently associated with complications in some reports [27–29]. However, patients with IPUD in the present study had no significant differences in clinical characteristics or complications when compared with patients that had either *H. pylori* or NSAID-associated PUD, with the exception that patients with *H. pylori* or NSAID-associated DU consumed more alcohol than those with IPUD. Little is known about the pathogenesis of IPUD and the literature is sparse. Some of these *H. pylori* negative ulcers might be caused by surreptitious use of NSAIDs or false-negative tests for *H. pylori* [30–32]. We also excluded patients with a history of ulcer disease to prevent misclassification of recurrent ulcers that had already received eradication therapy. In this study, idiopathic GU patients had significantly more bleeding complications than idiopathic DU patients. This finding means that IPUD will become a more important clinical issue. More studies to search for the pathogenesis and clinical significance of IPUD are warranted.

The limitation of this study was that comparison with our results from ten years ago might be inappropriate, because this study was a multi-center study and our previous study was a single-center study. But the changing trend of the prevalence of *H. pylori* infection and the distribution of PUD was similar over a period of ten years in the same hospital where the previous and current studies were performed (71.2 vs. 72.5%). A prospective population-based study in Korea is warranted.

In summary, in patients with PUD the proportion of DU decreased and that of GU increased during the last decade. The prevalence of *H. pylori* infection in GU and DU showed significant increasing and decreasing trends, respectively. IPUD in Korea was not uncommon and the clinical features and complications of IPUD were not significantly different from those of *H. pylori* or NSAID-associated PUD.

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