High Recurrence Rate of Idiopathic Peptic Ulcers in Long-Term Follow-up

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Background/Aims: Our aim was to compare the long-term clinical outcomes of idiopathic peptic ulcer disease (IPUD) with those of Helicobacter pylori-positive and nonsteroidal anti-inflammatory drug (NSAID)-induced peptic ulcer disease (PUD). Methods: Patients with endoscopically diagnosed PUD were retrospectively reviewed. According to their H. pylori-infection status and history of NSAIDs use, patients were categorized into three groups: H. pylori-positive PUD, NSAID-induced PUD, and IPUD. Clinical outcomes were analyzed, and the recurrence rate of PUD was compared among the three groups. Results: A total of 238 patients were enrolled. Those with IPUD, NSAID-induced PUD, and H. pylori-positive PUD comprised of 56, 60, and 122 patients, respectively. The 5-year cumulative incidences of recurrent ulcers were 24.3% (95% confidence interval [CI], 11.6% to 37.0%) in IPUD, 10.9% (95% CI, 2.6% to 19.2%) in NSAID-induced PUD, and 3.8% (95% CI, 0.1% to 7.5%) in H. pylori-positive PUD (IPUD vs NSAID-induced PUD/H. pylori-positive PUD, p=0.43/0.001 by log-rank test). In the Cox-proportional hazards model, only IPUD remained as an independent risk factor associated with recurrent ulcers (hazard ratio, 5.97; 95% CI, 1.94 to 18.34; p=0.002). Conclusions: IPUD exhibited a higher recurrence rate than H. pylori-positive and NSAID-induced PUD in long-term follow-up and was an independent risk factor for ulcer recurrence. [Gut Liver 2013;7:175-181]

Key Words: Helicobacter pylori; Idiopathic peptic ulcer; Nonsteroidal anti-inflammatory drug; Recurrence

INTRODUCTION

The discovery that Helicobacter pylori is associated with peptic ulcer recurrence was the turning point of peptic ulcer treatment. Eradication of H. pylori in the patients with peptic ulcer disease (PUD) has dramatically reduced the recurrence rate of disease. Aside from H. pylori infection, nonsteroidal anti-inflammatory drugs (NSAIDs) have been one of the leading causes of PUD. However, the definite cause of peptic ulcer cannot be identified in some patients in spite of comprehensive evaluation.

Idiopathic PUD (IPUD) is defined as a peptic ulcer without definite causes such as H. pylori infection, NSAIDs use or hypergastrinemia. The prevalence of IPUD remarkably varies from 1.3% to 27% with the background prevalence of H. pylori infection in the region. In Korea, recent study suggested that the proportion of IPUD in PUD was 22.2%. Considering that the prevalence of H. pylori infection has been decreasing, the proportion of IPUD in Korea is expected to increase furthermore.

However, the natural history and long-term clinical outcome of IPUD have not yet been well clarified. In cohort studies, the patients with IPUD have a high risk of recurrent ulcer bleeding and mortality, but the long-term clinical outcome of nonbleeding IPUD were not evaluated in regard to risk of ulcer recurrence. In another study, uncomplicated H. pylori-negative duodenal ulcers had high recurrence rate during 2-year follow-up, in which the sample size and the duration of follow-up was not enough to evaluate the long-term outcomes. Moreover, a history of NSAIDs use was not considered as possible etiology of peptic ulcer. A small-scaled study in China showed high recurrence rate of IPUD during several years of follow-up, however, the study subjects were children.

Therefore, the aim of this study was to compare the long-term recurrence rate of IPUD in adults with two major etiologic groups of PUD; H. pylori-positive PUD and NSAIDs-induced PUD.

MATERIALS AND METHODS

1. Patients

We identified patients over 18 years of age with a diagnosis code of peptic ulcer, benign gastric ulcer, or duodenal ulcer in...
2005 at Seoul National University Hospital, Seoul, South Korea through electronic medical records. Among identified 870 patients, 425 individuals were confirmed to have gastric or duodenal ulcer in the endoscopic finding. Ulcer was defined as a mucosal break with an apparent depth over 5 mm in diameter. In the next step, patients with history of partial gastrectomy, malignancy within the previous 5 years, ulcer in scar stage, malignant ulcer, endoscopic procedure-related ulcer, Dieulafoy’s ulcer, or no result of H. pylori infection status were excluded. Of the remaining 291 patients, after excluding 53 individuals who had less than 6 months of follow-up duration, finally 238 patients with PUD were analyzed. The Institutional Review Board of the Seoul National University Hospital approved this study.

2. Characteristics and etiologic categorization of PUD

Data about location, stage, and number of ulcers were retrospectively reviewed with electrical medical records for each patient. In cases where ulcers were found in both stomach and duodenum, organ with more prominent lesion was defined as ulcer location. The number of comorbid diseases was calculated by reviewing diagnosis codes in each patient. Types of drugs used to treat ulcers and treatment duration were also investigated. To collect the history of recent NSAIDs use, we scrutinized outpatient records and prescription list through electronic medical records system. For each patient, the status of H. pylori infection at the diagnosis of PUD was reviewed by the result of histology and rapid urease test (CLO test; Kimberly-Clark, Draper, UT, USA). Biopsy for histologic evaluation and rapid urease test was done in the ulcer margin and the antrum, respectively. H. pylori infection was defined as positive if at least one of two tests was positive. Because false negative results of rapid urease test can occur in patients taking antibiotics or proton pump inhibitors (PPIs), in cases where these drugs were prescribed in the preceding 4 weeks, patients without histological evaluation were excluded from the study.

Based on the etiology of PUD, patients were categorized into three groups: 1) NSAIDs-induced PUD group with history of regular NSAIDs or aspirin use within 1 month before diagnosis regardless of H. pylori infection status, 2) H. pylori-positive PUD group, and 3) IPUD group without the evidence of hypergastrinemia.

3. Follow-up

Initial event was defined as the day when a patient was diagnosed as PUD by endoscopy. In cases with gastric ulcer, follow-up endoscopy had been performed after 8 to 12 weeks of treatment to confirm the cure of ulcer, and when the patients had recurrent symptom with PUD. Recurrent ulcer was defined as gastric or duodenal ulcer of active or healing stage confirmed by endoscopy during the follow-up period. Terminal event was defined as the day when the recurrent ulcer was diagnosed or the last follow-up day to August 2010. The history of drug use including H. pylori eradication, NSAIDs, PPIs, or histamine 2 receptor antagonists (H2RAs) to the terminal event was scrutinized by the electronic medical records. Continued NSAIDs use was defined by the exposure to that drug for more than 50% of the follow-up period. In addition, new infection and eradication history of H. pylori during the follow-up period were also studied.

4. Statistical analysis

IBM SPSS for Windows version 18.0 (IBM, Armonk, NY, USA) was used for the statistical analysis. Baseline clinical characteristics of patients and analysis of ulcer recurrence were presented as descriptive data. Continuous variables were analyzed using Kruskal-Wallis test. In cases where there was significant difference in the three study groups, pairwise-comparisons were additionally done using Mann-Whitney U test. The chi-square test or Fisher’s exact test were used to analyze categorical variables. Cumulative probabilities of ulcer recurrence were estimated by the Kaplan-Meier method. The log-rank test was used to compare time-to-event curves between the three groups. A Cox-proportional hazards model was used to identify possible covariates as significant predictors of ulcer recurrence which included sex, age (≥60 years), number of comorbid diseases (≥2), location of ulcer (gastric vs duodenal), duration of ulcer treatment (≥9 weeks), H. pylori infection status, and concomitant use of NSAIDs. All results were considered statistically significant when p-values were less than 0.05.

RESULTS

1. Baseline clinical characteristics

Among a total of 238 patients, H. pylori-positive PUD, NSAIDs-induced PUD, and IPUD were 122 (51.3%), 60 (25.2%), and 56 (23.5%), respectively (Table 1). NSAIDs-induced PUD group was significantly older than H. pylori-positive PUD group (p<0.001). The rate of patients with comorbid diseases more than one was significantly higher in NSAIDs-induced PUD group than in other groups (NSAIDs-induced PUD vs H. pylori-positive PUD and IPUD, p<0.001 and p=0.005). Patients with H. pylori-positive PUD had a higher proportion of duodenal ulcer than other groups (H. pylori-positive PUD vs NSAIDs-induced PUD and IPUD, p=0.002 and p<0.001). The most commonly used medicine for the treatment of ulcer was PPIs (177/238, 74.4%) and patients with IPUD were treated for a longer period than patients with H. pylori-positive PUD (p<0.001).

2. Follow-up and ulcer recurrence

Table 2 shows analysis of follow-up and ulcer recurrence in the three groups. The follow-up duration of NSAIDs-induced PUD group was longer than that of H. pylori-positive PUD group (p<0.001). IPUD group had more follow-up endoscopies than H. pylori-positive PUD group (p=0.009). During follow-